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(22) Date of filing: **27.09.1991**

(54) **Novel sulfonamide fibrinogen receptor antagonists**

Neue Sulfonamid-Fibrinogen-Rezeptor-Antagonisten

Nouveaux sulfonamides comme antagonistes des récepteurs fibrinogéniques

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(56) References cited:
EP-A- 0 004 011

Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

EP 0 478 363 B1

Description

BACKGROUND OF THE INVENTION

The present invention provides novel compounds, novel compositions, methods of their use and methods of their manufacture, such compounds being generally pharmacologically useful as anti-platelet aggregation agents in various vascular pathologies. The aforementioned pharmacologic activities are useful in the treatment of mammals. More specifically, the sulfonamide compounds of the present invention act by blocking the molecular receptor site of the protein fibrinogen. Fibrinogen is a glycoprotein that circulates in the blood plasma, and whose platelet receptor site is glycoprotein IIb/IIIa. By blocking the action of fibrinogen at the receptor (glycoprotein IIb/IIIa), the compounds of the present invention interfere with platelet aggregation, which is a cause of many vascular pathologies. At the present time, there is a need in the area of vascular therapeutics for such a fibrinogen receptor blocking agent. By interfering with hemostasis, such therapy would decrease the morbidity and mortality of thrombotic disease.

Hemostasis is the spontaneous process of stopping bleeding from damaged blood vessels. Precapillary vessels contract immediately when cut. Within seconds, thrombocytes, or blood platelets, are bound to the exposed matrix of the injured vessel by a process called platelet adhesion. Platelets also stick to each other in a phenomenon known as platelet aggregation to form a platelet plug. This platelet plug can stop bleeding quickly, but it must be reinforced by the protein fibrin for long-term effectiveness, until the blood vessel tear can be permanently repaired by growth of fibroblasts, which are specialized tissue repair cells.

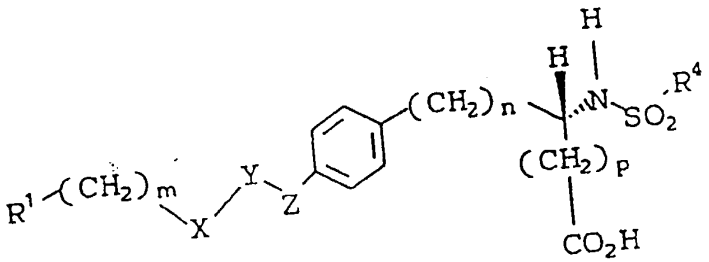
An intravascular thrombus (clot) results from a pathological disturbance of hemostasis. The thrombus can grow to sufficient size to block off arterial blood vessels. Thrombi can also form in areas of stasis or slow blood flow in veins. Venous thrombi can easily detach portions of themselves called emboli that travel through the circulatory system and can result in blockade of other vessels, such as pulmonary arteries. Thus, arterial thrombi cause serious disease by local blockade, whereas venous thrombi do so primarily by distant blockade, or embolization. These diseases include venous thrombosis, thrombophlebitis, arterial embolism, coronary and cerebral arterial thrombosis and myocardial infarction, stroke, cerebral embolism, kidney embolisms and pulmonary embolisms.

There is a need in the area of cardiovascular and cerebrovascular therapeutics for an agent which can be used in the prevention and treatment of thrombi, with minimal side effects, including unwanted prolongation of bleeding in other parts of the circulation while preventing or treating target thrombi. The compounds of the present invention meet this need in the art by providing therapeutic agents for the prevention and treatment of thrombi.

The compounds of the present invention show efficacy as antithrombotic agents by virtue of their ability to block fibrinogen from acting at its platelet receptor site and thus prevent platelet aggregation.

EP-A-004001 discloses a class of phenoxyalkyl carboxylic acids which may be of use in lowering serum lipids but contains no suggestion that compound containing a phenylalkyl carboxylic moiety could be prepared.

The present invention provides compounds of the structural formula:



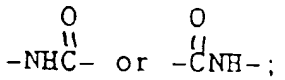
or a pharmaceutically acceptable salt thereof, wherein

R^1 is a six member saturated heterocyclic ring containing one or two heteroatoms wherein said heteroatoms are N or 0 and wherein said heterocyclic ring is optionally substituted by C_{1-3} alkyl; or

NR^6R^7 wherein R^6 and R^7 are independently hydrogen or C_{1-10} alkyl;

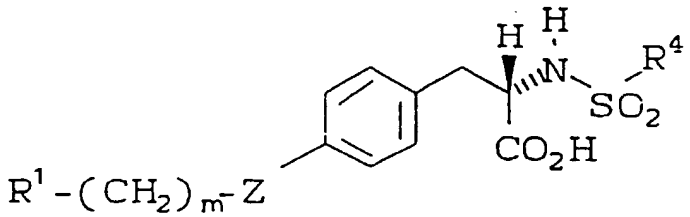
R^4 is aryl, C_{1-10} alkyl or C_{4-10} aralkyl ;

X and Y areindependently C_{1-10} alkyl or cycloalkyl,



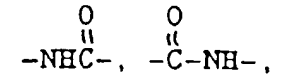
Z is an optional substituent that, when present, is O, NHC(O), -C(O)NH- or C_{1-5} straight or branched alkyl;
m is an integer of from zero to six;
n is one or two; and
p is zero or one.

Preferred compounds of the invention are are of the structural formula:



or a pharmaceutically acceptable salt thereof,
wherein

R^1 is a six member saturated heterocyclic ring containing one or two heteroatoms wherein said heteroatoms are N;
NR^6R^7 wherein R^6 and R^7 are independently
H or
C_{1-10} alkyl;
R^4 is aryl
C_{1-10} alkyl
C_{4-10} aralkyl;
Z is O,



where m is an integer from two to six.

DETAILED DESCRIPTION OF THE INVENTION

The term "pharmaceutically acceptable salts" shall mean non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid. Representative salts include the following salts:

Acetate
Benzenesulfonate
Benzoate
Bicarbonate
Bisulfate
Bitartrate
Borate
Bromide
Calcium Edetate
Camsylate

Carbonate
Chloride
Clavulanate
Citrate
Dihydrochloride
Edetate
Edisylate
Estolate
Esylate
Fumarate
Gluceptate
Gluconate
Glutamate
Glycollylarsanilate
Hexylresorcinate
Hydrabamine
Hydrobromide
Hydrochloride
Hydroxynaphthoate
Iodide
Isothionate
Lactate
Lactobionate
Laurate
Malate
Maleate
Mandelate
Mesylate
Methylbromide
Methylnitrate
Methylsulfate
Mucate
Napsylate
Nitrate
Oleate
Oxalate
Pamaote
Palmitate
Pantothenate
Phosphate/diphosphate
Polygalacturonate
Salicylate
Stearate
Subacetate
Succinate
Tannate
Tartrate
Teoclate
Tosylate
Triethiodide
Valerate

The term "pharmacologically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical reponse of a tissue, system or animal that is being sought by a researcher or clinician. The term "anti-coagulant agent" shall include aspirin, heparin and warfarin. The term "fibrinolytic agent" shall include streptokinase and tissue plasminogen activator.

The term "aryl" shall mean a mono- or polycylic ring system composed of 5- and 6- membered aromatic rings containing 0, 1, 2, 3, or 4 heteroatoms chosen from N, O, and S and either unsubstitutued or substituted with R^6.

The term "alkyl" shall mean straight or branched chain alkane, alkene or alkyne.

The term "alkoxy" shall be taken to include an alkyl portion where alkyl is as defined above.

The terms "aralkyl" and "alkaryl" shall be taken to include an alkyl portion where alkyl is as defined above and to include an aryl portion where aryl is as defined above.

The term "halogen" shall include fluorine, chlorine, iodine and bromine.

The term "oxo" shall mean the radical =O.

The term "thio" shall mean the radical =S.

Compounds of the invention may be administered to patients where prevention of thrombosis by inhibiting binding of fibrinogen to the platelet membrane glycoprotein complex IIb/IIIa receptor is desired. They are useful in surgery on peripheral arteries (arterial grafts, carotid endarterectomy) and in cardivascular surgery where manipulation of arteries and organs, and/or the interaction of platelets with artificial surfaces, leads to platelet aggregation and consumption. The aggregated platelets may form thrombi and thromboemboli. They may be administered to these surgical patients to prevent the formation of thrombi and thromboemboli.

Extracorporeal circulation is routinely used for cardivascular surgery in order to oxygenate blood. Platelets adhere to surfaces of the extracorporeal circuit. Adhesion is dependent on the interaction between GPIIb/IIIa on the platelet membranes and fibrinogen adsorbed to the surface of the circuit. (Gluszko et. al., Amer. J. Physiol., 1987, 252:H, pp 615-621). Platelets released from artificial surfaces show impaired hemostatic function. Compounds of the invention may be administered to prevent adhesion.

Other application of these compounds include prevention of platelet thrombosis, thromboembolism and reocclusion during and after thrombolytic therapy and prevention of platelet thrombosis, thromboembolism and reocclusion after angioplasty of coronary and other arteries and after coronary artery bypass procedures. They may also be used to prevent mycocardial infarction.

The compounds of the present invention can be administered in such oral dosage forms as tablets, capsules, pills, powders, granules, elixers, tinctures, suspensions, syrups and emulsions. Likewise, they may also be administered in intravenous, intraperitoneal, subcutaneous or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as an anti-aggregation agent.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

Oral dosages of the present invention, when used for the indicated effects, will range between about 0.01 mg per kg of body weight per day (mg/kg/day) to about 100 mg/kg/day and preferably 1.0-100 mg/kg/day and most preferably 1.0 to 50 mg/kg/day. Intravenously, the most preferred doses will range from about 1 to about 10 mg/kg/minute during a constant rate infusion. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittant throughout the dosage regimen.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as 'carrier' materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesuim stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a

variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

The compounds of the present invention can also be co-administered with suitable anti-coagulant agents or thrombolytic agents to achieve synergistic effects in the treatment of various vascular pathologies.

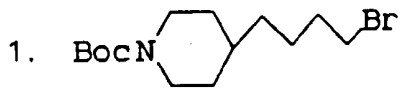
The compounds of formula I can be prepared readily according to the following reaction Schemes and Examples or modifications thereof using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail.

The most preferred compounds of the invention are any or all of those specifically set forth in these examples. These compounds are not, however, to be construed as forming the only genus that is considered as the invention, and any combination of the compounds or their moieties may itself form a genus. The following examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative precedures can be used to prepare these compounds. All temperatures are degrees Celsius unless noted otherwise.

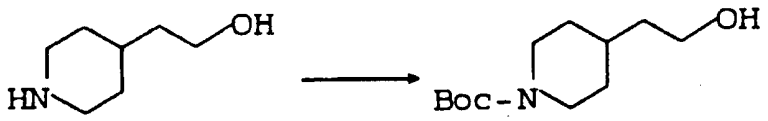
Reagent symbols have the following meanings:

BOC:	t-butyloxycarbonyl
Pd-C:	Palladium on activated carbon catalyst
DMF:	Dimethylformamide
DMSO:	Dimethylsulfoxide
CBZ:	Carbobenzyloxy
CH_2Cl_2:	Methylene chloride
$CHCl_3$:	Chloroform
EtOH:	Ethanol
MeOH:	Methanol
EtOAc:	Ethyl acetate
HOAc:	Acetic acid
THF:	Tetrahydrofuran

The source for the following compounds is as shown:

1. 

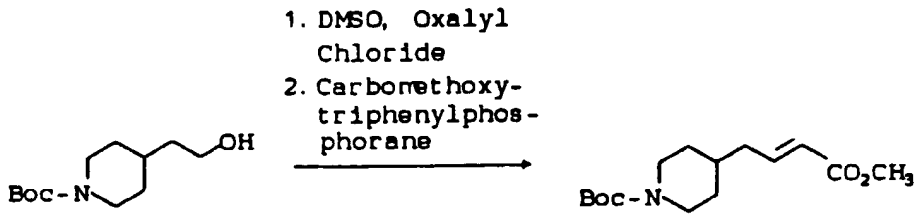
is described below.



2-(4-N-t-Butyloxycarbonylpiperidinyl)ethanol

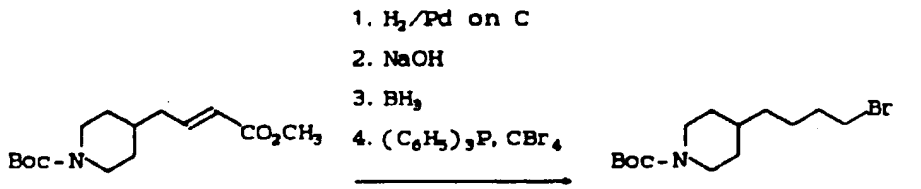
4-Piperidine-2-ethanol (Available from Aldrich) (130 g, 1.0 mole) was dissolved in 700 mL dioxane, cooled to 0° C and treated with 3 N NaOH (336 mL, 1.0 mole), and di-t-butylcarbonate (221.8 g, 1.0 mole). The ice bath was removed and the reaction stirred overnight. The reaction was concentrated, diluted with water and extracted with ether. The ether layers were combined, washed with brine, dried over $MgSO_4$, filtered and evaporated to give 225.8 g of product

(98%).
R_f = 0.37 in 1:1 EtOAc/Hexanes, ninhydrin stain
^1H NMR (300MHz, $CDCl_3$) δ 4.07 (bs, 2H), 3.7 (bs, 2H), 2.7 (t, J = 12.5 Hz, 2H), 1.8-1.6 (m, 6H), 1.51 (s, 9H), 1.1 (ddd, J = 4.3, 12.5, 12 Hz, 2H).



Methyl 4-(4-N-t-butyloxycarbonylpiperidinyl)-but-2-enoate

Oxalyl chloride (55.8 mL, 0.64 mole) was dissolved in 1 L CH_2Cl_2 and cooled to -78° C under N_2. DMSO (54.2 mL, 0.76 mole) was added dropwise. After gas evolution had ceased, 2-(4-N-t-butyloxycarbonylpiperidinyl)ethanol (102.5 g, 0.45 mole) dissolved in 200 mL CH_2Cl_2 was added over 20 minutes. After stirring an additional 20 minutes, triethylamine (213 mL, 1.53 mole) was added dropwise and the cold bath removed. After 1 and 1/2 hours TLC showed starting material gone. Carbomethoxytriphenylphosphorane (179 g, 0.536 mole) was added and the reaction stirred overnight. The solution was diluted with 300 mL Et_2O, extracted once with 800 mL H_2O, twice with 300 mL 10% $KHSO_4$ solution, then once with 300 mL brine. The organic layer was dried over $MgSO_4$, filtered and evaporated. Column chromatography (SiO_2, 5% EtOAc/Hexanes) yielded 78.4 g (62%) of pure methyl 4-(4-N-t-butyloxycarbonylpiperidinyl) but-2-enoate.
^1H NMR (300MHz, $CDCl_3$) δ 6.9 (ddd J = 15.6, 7,6, 7.6 Hz, 1H), 5.8 (d, J = 15.6 Hz, 1H), 4.0 (bs, 2H), 3.7 (s, 3H), 2.6 (t, J = 12.6 Hz, 2H), 2.1 (t, J = 7.4 Hz, 2H), 1.7-1.4 (m, 3H), 1.4 (s, 9H), 1.1 (m, 2H).



4-(4-N-t-Butyloxycarbonylpiperidinyl)butyl bromide

Methyl 4-(4-N-t-butyloxycarbonylpiperidinyl)but-2-enoate (36.2 g, 0.128 mole), was dissolved in 500 mL EtOAc. 10% Palladium on carbon (10 g) was added as a slurry in EtOAc and the reaction was placed under H_2 (in a balloon) overnight. The reaction was filtered through Solka-Floc, the cake washed with EtOAc and the ethyl acetate evaporated to give 34.7 g (90%) of methyl 4-(4-N-t-butyloxycarbonylpiperidin-4-yl)butanoate. TLC R_f = 0.69 in 30% EtOAc/Hexanes.

^1H NMR (300MHz, $CDCl_3$) δ 4.0 (bs, 2H), 3.6 (s, 3H), 2.60 (t, J = 12.3 Hz, 2H), 2.20 (t, J = 7.4, 2H), 1.6 (m, 4H), 1.40 (s, 9H), 1.40 (m, 1H), 1.20 (m, 2H), 1.0 (m, 2H).

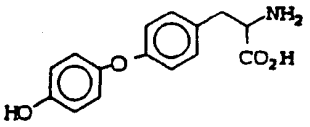
The butanoate ester (45.3 g, 0.159 mole) was dissolved in CH_3OH and treated with 1 N NaOH (500 mL, 0.5 mole) overnight. The solvent was removed in vacuo, water was added and the solution washed with ether, then acidified with 10% $KHSO_4$ solution. The aqueous layer was washed with ether, the ether layers were combined, washed with brine, dried ($MgSO_4$), and concentrated to give the corresponding acid as a clear oil (41.85 g, 97% yield).
^1H NMR (300MHz, $CDCl_3$) δ 4.0 (bs, 2H), 2.6 (m, 2H), 2.25 (m, 2H), 1.6 (bs, 4H, 1.4 (s, 9H), 1.3-0.9 (9H).

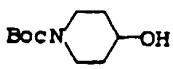
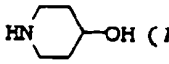
This acid (20.4 g, 0.077 mole) was treated with borane (BH_3/THF, 235 mL, 235 mmole) in THF at 0° for 1 hour. NaOH (1N, 250 mL) was added dropwise and the solution stirred overnight. The resulting reaction mixture was concentrated to remove THF and extracted with ether. The ether extracts were combined, dried over $MgSO_4$, filtered and evaporated to give the corresponding alcohol as 19.7 g of a colorless oil.

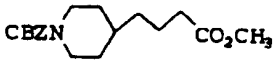
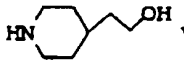
R_f = 0.7 in 2:1 ethyl acetate/hexanes.
^{1}H NMR (300MHz, $CDCl_3$) δ 4.1 (bs, 2H), 3.6 (t, 2H), 2.65 (t, 2H), 2.1 (bs, 1H), 1.65 (bs, 2H), 1.55 (m, 2H), 1.4 (s, 9H), 1.35 (m, 3H), 1.25 (m, 2H), 1.1 (m, 2H).

This alcohol (19.7 g, 76.5 mmole) was dissolved in THF and treated with triphenylphosphine (23.1 g, 88 mmole) and cooled to 0° C. Carbon tetrabromide (29.8 g, 89.9 mmol) was added in one portion, the cold bath was removed and the reaction stirred overnight. Additional triphenyl phosphine (11.71 g) and carbon tetrabromide (14.9 g) was added to drive the reaction to completion. The mixture was filtered and the liquid was diluted with ether and filtered again. After solvent removal the resulting liquid was adsorbed onto SiO_2 and chromatographed with 5% EtOAc/Hexanes to yield 4-(4-N-t-butyloxycarbonylpiperidin-4-yl)butyl bromide as a clear colorless oil (20.7 g, 85% yield).
R_f = 0.6 in 1:4 ethyl acetate/hexanes
^{1}H NMR (300MHz, $CDCl_3$) δ 4.1 (bs, 2H), 3.4 (t, 2H), 2.65 (t, 2H), 1.85 (m, 2H), 1.65 (bd, 2H), 1.4 (s, 9H), 1.35 (m, 2H), 1.3 (m, 3H), 1.1 (m, 2H).

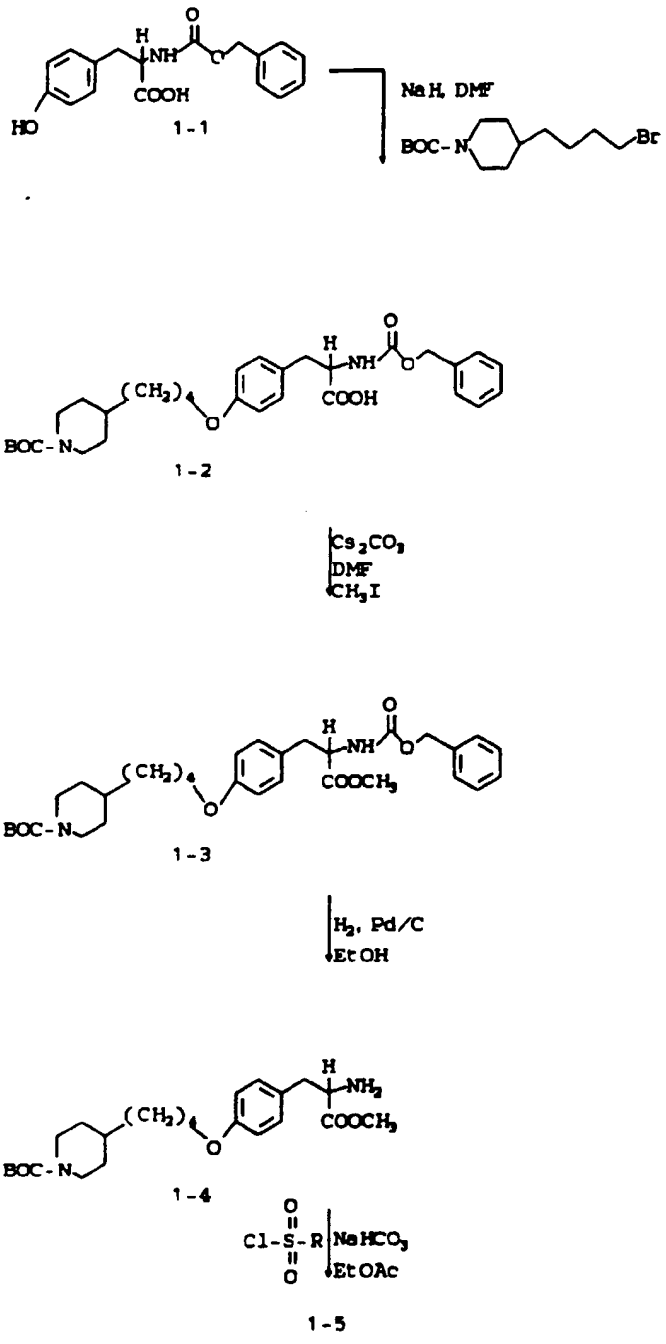
2. $BocNH(CH_2)_6Br$ Commercial $H_2N(CH_2)_5CH_2OH$ was protected as the N-Boc derivative in standard fashion and this was converted to the bromide with Ph_3P/CBr_4 in THF. Utilization of starting amino alcohols of varying chain lengths provides the analogous halides in this manner.

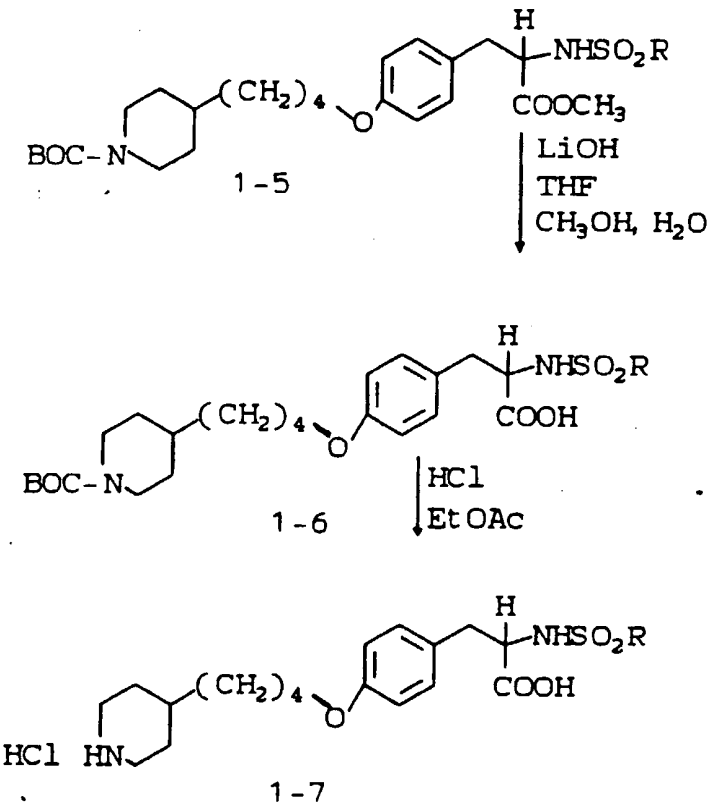
3.  Purchased from Sigma.

4.   (Aldrich) was N-Boc protected in the standard manner.

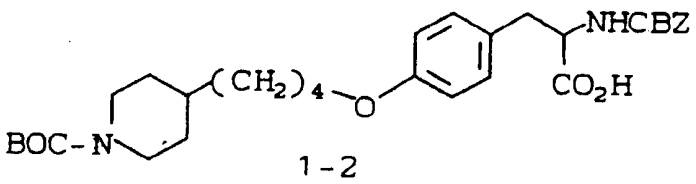
5.   was N-Cbz protected in the standard fashion and converted to final product as described in US Serial No. 589,145.

SCHEME 1


NaH, DMF
BOC-N
Br
HO
COOH
1-1
1-2
Cs_2CO_3
DMF
CH_3I
$COOCH_3$
1-3
H_2, Pd/C
EtOH
NH_2
1-4
$NaHCO_3$
EtOAc
1-5



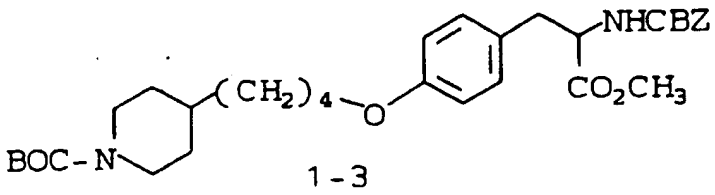
EXAMPLE 1



2-S-(Benzyloxycarbonylamino)-3-[4-(N-t-butyloxycarbonylpiperidin-4-yl)butyloxyphenyl]propionic acid (1-2)

N-CBZ-L-tyrosine (1-1) (17.58 g, 0.055 mmole) was dissolved in DMF (75 mL), cooled to 0-10° C and treated with sodium hydride (2.88 g, 0.12 mole). This suspension was stirred at 0-10° C for 1 hour and then N-t-butyloxycarbonyl-piperidin-4-ylbutyl bromide (17.70 g, 0.055 mole) in 25 mL DMF was added dropwise over 15 minutes. The reaction mixture was then stirred at room temperature for 16 hours. The solvent was removed in vacuo and the residue was taken up in a mixture of 500 mL EtOAc/100 mL 10% $KHSO_4$. The organic phase was washed with brine, dried (Na_2SO_4) and the solvent was removed to give a viscous oil. This was purified by flash chromatography on silica gel eluting with 98:2:0.5 $CHCl_3/CH_3OH$/HOAc to give pure 1-2 (23.75 g), R_f = 0.35, as a pale yellow oil.
^1H NMR (300MHz, $CDCl_3$) δ 1.00-1.15 (2H, m), 1.20-1.80 (16H, m), 2.62 (2H, t), 3.10 (2H, m), 3.91 (2H, t), 4.04 (2H, m), 5.10 (2H, m), 5.22 (1H, d), 6.78 (2, d), 7.04 (2H, d), 7.35 (5H, m).

EXAMPLE 2



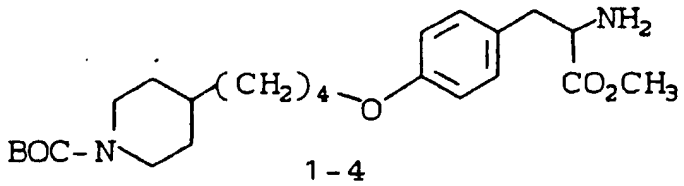
1-3

Methyl 2-S-(Benzyloxycarbonylamino)-3-[4-(N-t-butyloxycarbonylpiperidin-4-yl)butyloxyphenyl]propionic acid (1-3)

1-2 (10.05 g, 18.1 mmole) was dissolved in CH_3OH (150 mL) at room temperature and cesium carbonate (2.95 g, 9.06 mmole) was added and the resulting mixture stirred for 15 minutes to give a clear solution. The CH_3OH was removed at reduced pressure and the residue was then dissolved in DMF (150 mL) and treated dropwise with methyl iodide (2.57), 18.1 mmole). The resulting solution was stirred overnight at room temperature. The solvent was removed in vacuo and the residue was taken up in 400 mL ether and washed with 3 x 50 mL portions of H_2O, 50 mL brine and dried (Na_2SO_4). Solvent removal provided 1-3 as an oil.

^1H NMR (300 MHz, $CDCl_3$) δ 1.0-1.15 (2H, m), 1.30-1.70 (16H, m), 2.68 (2H, dt), 3.05 (2H, m), 3.72 (3H, s), 3.91 (2H, t), 4.08 (2H, d), 4.61 (1H, m), 5.10 (2H, m), 5.18 (1H, m), 6.79 (2H, d), 6.98 (2H, d), 7.35 (5H, m).

EXAMPLE 3



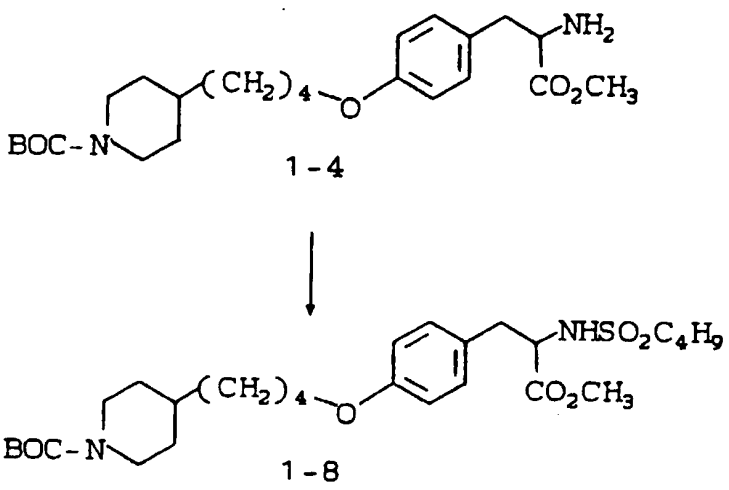
1-4

Methyl 2-S-Amino-3-[4-(N-t-butyloxycarbonylpiperidin-4-yl)-butyloxyphenyl]propionate (1-4)

To 1-3 (5.0 g, 8.79 mmole) dissolved in absolute ethanol (150 mL) was added 10% Pd/C (0.5 g) and the resulting suspension was hydrogenated under balloon pressure for 12 hours. The catalyst was then filtered off and the solvent was removed in vacuo to give 1-4 (3.6 g) as an oil.

^1H NMR (300 MHz, $CDCl_3$) δ 1.00-1.20 (2H, m), 1.22-1.55 (12H, m), 1.60-1.75 (4H, m), 2.00 (2H, bs), 2.68 (2H, t), 2.87 (1H, dd), 3.05 (1H, dd), 3.72 (3H, s), 3.93 (2H, t), 4.09 (2H, m), 6.82 (2H, d), 7.10 (2H, d).

EXAMPLE 4

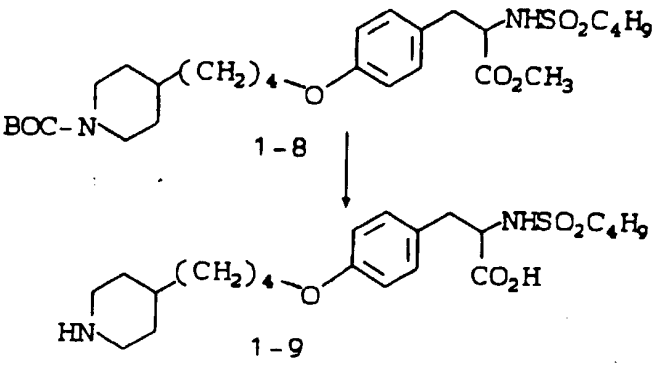


Methyl 2-S-(n-Butylsulfonylamino)-3-[4-(N-t-butyloxycarbonylpiperidin-4-yl)butyloxyphenyl]propionate (1-8)

1-4 (0.59 g, 1.36 mmole) was dissolved in ethyl acetate (10 mL) and $NaHCO_3$ (0.7 g, 8.68 mmole) was added with stirring at room temperature followed by butanesulfonyl chloride (0.36 mL, 2.76 mmole) and the resulting mixture was refluxed for 26 hours. The cooled reaction mixture was filtered and concentrated and the residue was purified by flash chromatography on silica gel eluting with 4:1 hexane/EtOAc to give pure 1-8 (0.305 g) $R_f = 0.7$ in 1:1 hexane/EtOAc, ninhydrin stain.

^1H NMR (300 MHz, $CDCl_3$) δ 0.82 (3H, t), 1.05 (2H, ddd), 1.45 (9H, s), 1.1-1.6 (1H, m), 1.7 (4H, m), 2.6 (2H, t), 2.6-2.8 (2H, m), 2.78 (1H, dd), 3.05 (1H, dd), 3.7 (3H, s), 3.93 (2H, t), 4.05 (2H, bd), 4.15 (1H, dd), 6.85 (2H, d), 7.15 (2H,d).

EXAMPLE 5

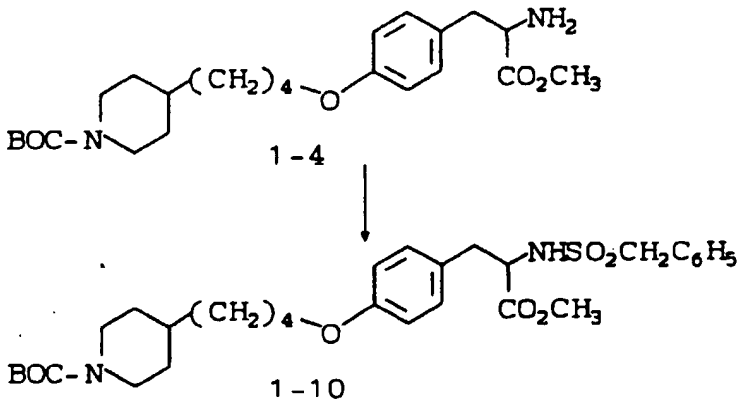


2-S-(n-Butylsulfonylamino)-3[4-(piperidin-4-yl)butyloxyphenyl]propionic acid hydrochloride (1-9)

1-8 (0.325 g, 0.59 mmole) was dissolved in 1:1:1 CH_3OH/H_2O/THF and $LiOH{\cdot}H_2O$ (0.157g, 3.76 mmole) was added. The resulting solution was stirred at room temperature for 3 hours, then concentrated, diluted with 10% $KHSO_4$ and extracted with EtOAc. This provided 2-S-(n-butylsulfonylamino)-3[4-(N-t-butyloxycarbonylpiperidin-4-yl)butyloxyphenyl]propionic acid. This acid (0.315 g, 0.59 mmole) was dissolved in EtOAc (20 mL) and treated with HCl gas at -20° C for 15 minutes. The reaction mixture was then stoppered and was stirred at -5° C for 1 hour at which time all starting material was consumed. Argon gas was bubbled through the reaction mixture for 15 minutes and the solvent was removed to give a residue that was triturated with ether to provide pure 1-9 (0.29 g) as a pale yellow solid.

^{1}H NMR (300 MHz, CD_3OD) δ 0.85 (3H,t), 1.2 (2H,dd), 1.2-1.7 (9H,m), 1.7 (2H, m), 1.95 (2H, bs), 2.65 (2H, t), 2.8 (1H, dd), 2.95 (2H, bt), 3.10 (1H, dd), 3.83 (2H, bs), 3.95 (2H, t), 4.1 (1H, dd), 6.85 (2H, d), 7.2 (2H, d).
Analysis for $C_{22}H_{36}N_2O_5$1S·HCl·0.8 H_2O
Calculated: C = 53.76, H = 7.92, N = 5.70
Found: C = 53.76, H = 7.66, N = 5.44.

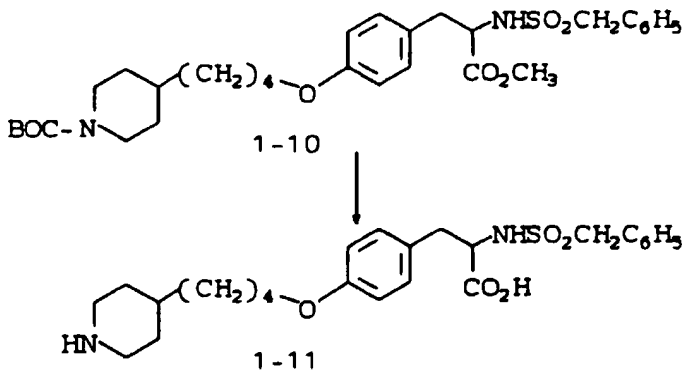
EXAMPLE 6



Methyl 2-S-(Benzylsulfonylamino)-3-[4-(N-t-butyloxycarbonylpiperidin-4-yl)butyloxyphenyl]propionate (1-10)

1-4 (0.59g, 1.36 mmole) was treated with benzylsulfonyl chloride (0.263 g, 1.38 mmole) as described above for 1-8. The crude reaction product was purified by flash chromatography on silica gel eluting with 3:1 hexane/EtOAc to give pure 1-10 (0.35 g) as an oil.
^{1}H NMR (300 MHz, CD_3OD) δ 0.85-1.10 (2H, m), 1.10-1.23 (2H,m), 1.35-1.52 (11H, m), 1.61-1.80 (4H, m), 2.65-3.00 (4H, m), 3.65 (3H, s), 3.90-4.14 (5H, m), 6.85 (2H, d), 7.08 (2H, d), 7.22 (2H, m), 7.30 (3H, m).

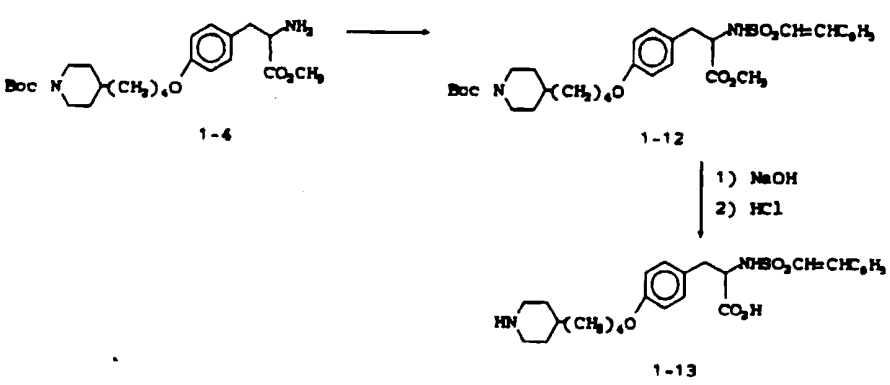
EXAMPLE 7



2-S-(Benzylsulfonylamino)-3-[4-(piperidin-4-yl)butyl-oxyphenyl]propionic acid hydrochloride (1-11)

Treatment of 1-10 (0.354 g, 0.60 mmole) with liOH (0.15 g, 3.7 mmole) as described for 1-8 gave 2-S-(benzylsulfonylamino)-3-[4-(N-t-butyloxycarbonylpiperidin-4-yl)butyloxyphenyl]propionic acid (0.35 g) as a viscous oil.
^{1}H NMR (300MHz CD_3OD) δ 0.84-1.06 (3H, m), 1.23 (4H, m), 1.34-1.50 (11H, m), 1.60-1.78 (5H, m), 2.65 (2H, bt), 2.82 (1H, m), 3.02 (1H, m), 3.91 (2H, m), 3.96-4.12 (5H, m), 6.83 (2H, d), 7.15 (2H, d), 7.22 (2H, m), 7.29 (3H, m).
This acid (0.35 g, 0.60 mmole) was dissolved in 20 mL EtOAc and treated with HCl gas as described for 1-9 to give pure 1-11 as a white solid (0.30 g).
^{1}H NMR (300MHz, CD_3OD) δ 1.32 (4H, m), 1.40-1.65 (3H, m), 1.72 (2H, m), 1.92 (2H, d), 2.77-3.08 (4H, m), 3.33 (3H,

m), 3.95-4.14 (5H, m), 6.86 (2H, d), 7.17 (2H, d), 7.28 (2H, m), 7.31 (3H, m).



Methyl 2-S-(2-Styrylsulfonylamino)-3-[4-(N-t-butyloxycarbonylpiperidin-4-yl)butyloxyphenyl]propionate (1-12)

1-4 (0.647 g, 15 mmoles) was dissolved in ethyl acetate (20 ml), and $NaHCO_3$ (0.454 g, 5.4 mmoles) was added followed by β-styrenesulfonyl chloride (0.365 g, 18.0 mmoles) and the resulting reaction mixture was heated at reflux with stirring for 16 hours. The cooled reaction mixture was filtered, the solvent removed and the residue was purified by flash chromatography on silica gel eluting with hexane (3)/ethyl acetate (1) to give pure 1-12.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (2H, m), 1.30-1.55 (14 H, m), 1.65-1.80 (4H, m), 2.68 (2H, t), 3.01 (2H, dt), 3.62 (3H, s), 3.88 (2H, t), 4.09 (2H, m), 4.22 (1H, m), 4.98 (1H, d), 6.45 (1H, d), 6.80 (2H, d), 7.06 (2H, d), 7.40 (4H, s).

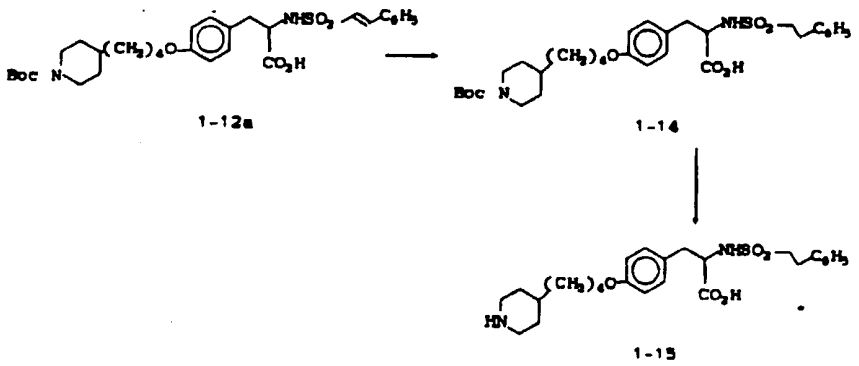
2-S-(2-Styrylsulfonylamino)-3-4-[4-piperidinylbutyloxyphenyl)propionic acid hydrochloride (1-13)

1-12 (0.58 g, 0.97 mmole) was dissolved in THF(1)-H_2O(1)-MeOH(1) (15 ml) and lithium hydroxide (0.12 g, 5.0 mmole) was added and the resulting clear solution was stirred overnight at room temperature.

The reaction mixture was diluted with 75 ml H_2O, acidfied to pH 2-3 with 10% $KHSO_4$ solution and then extracted with 3 x 50 ml EtOAc. The organic extract was dried, the solvent removed, and the residue purified by flash chromatography on silica gel eluting with $CHCl_3$(97)-MeOH(3)-HOAc(1) to give the desired acid (R_f=0.2).

This acid was dissolved in EtOAc and treated with HCl gas as described for 1-9 to give 1-13.

^{1}H NMR (300 MHz, CD_3OD) δ 1.15-1.70 (10H, m), 1.70-1.82 (2H, t), 1.97 (2H, t), 2.78-3.12 (5H, m), 3.35 (3H, m), 3.87 (2H, t), 4.03 (1H, m), 6.50 (1H, d), 6.69 (2H, m), 7.18 (3H, m), 7.41 (5H, bs).



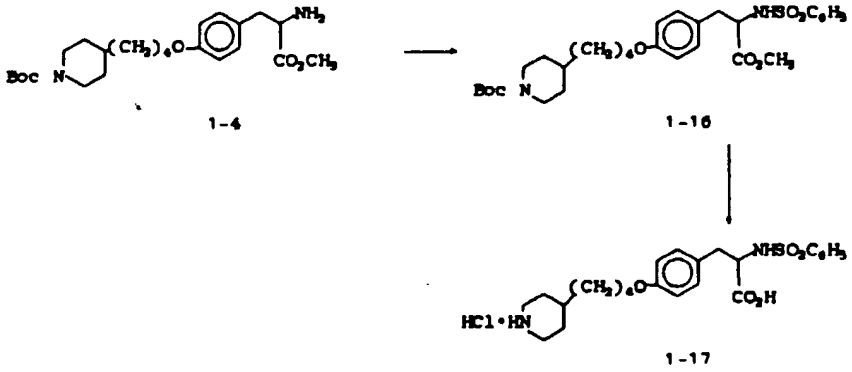
2-S-(2-Phenethylsulfonylamino)-3-[4-(N-t-butyloxycarbonylpiperidin-4-yl)butyloxyphenyl]propionic acid (1-14)

1-12a (0.21 g) was dissolved in 20 ml absolute ethanol, 0.1 g 10% Pd/C was added and the stirred suspension was hydrogenated under balloon pressure. After 4 hours the reaction was stopped and the solvent was removed to

give the desired product 1-14 (0.194 g).
^{1}H NMR (300 MHz, CD_3OD) δ 1.05 (2H, m), 1.30-1.40 (3H, m), 1.47 (14H, m), 1.72 (5H, m), 2.67-2.93 (8H, m), 3.13 (1H, m), 3.31 (2H, m), 3.82 (2H, m), 4.00-4.20 (4H, m), 6.82 (2H, d), 7.07 (2H, d), 7.21 (5H, m).

2-S-(2-Phenethylsulfonylamino)-3-4-[4-piperidinylbutyloxyphenyl]propionic acid hydrochloride (1-15)

1-14 (0.194 g) was dissolved in EtOAc and treated with HCl gas as described for 1-9 to provide pure 1-15 (0.145 g).
^{1}H NMR (300 MHz, CD_3OD) δ 1.25-1.68 (8H, m), 1.73 (2H, m), 1.93 (2H, m), 2.78 (3H, m), 2.91 (4H, m), 3.13 (1H, m), 3.33 (4H, m), 3.86 (2H, m), 4.18 (1H, m), 6.80 (2H, d), 7.09 (2H, d), 7.22 (5H, m).



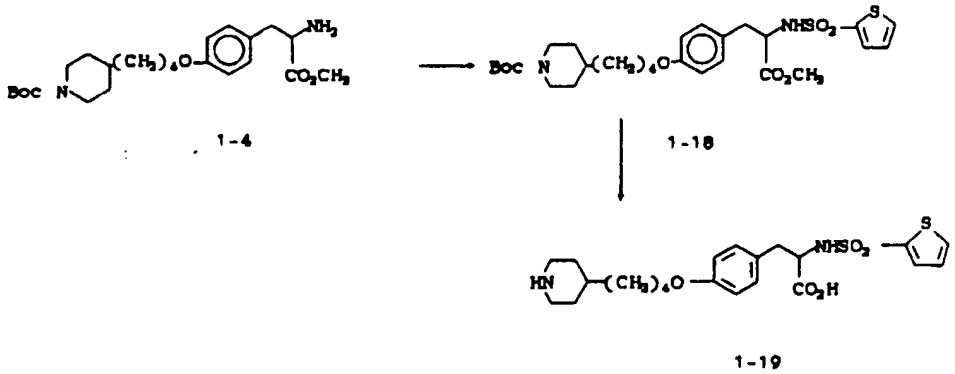
1-4 → 1-16 → 1-17

Methyl 2-S-(Phenylsulfonylamino)-3-[4-(N-t-butyloxycarbonylpiperidin-4-yl)butyloxyphenyl]propionate (1-16).

1-4 (0.647 g, 1.5 mmoles) was treated with phenylsulfonyl chloride (0.318 g, 1.8 mmoles) as described for 1-8. The crude product was purified by flash chromatography on silica gel eluting with $CHCl_3$(98)-MeOH(2) to give pure 1-16 (0.67 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (2H, m), 1.25-1.40 (3H, m), 1.42 (9H, bs), 1.60-1.85 (6H, m), 2.66 (2H, m), 2.96 (2H, d), 3.55 (3H, s), 3.89 (2H, t), 4.09 (4H, m), 5.12 (1H, d), 6.72 (2H, d), 6.95 (2H, d), 7.40-7.65 (3H, m), 7.75 (2H, m).

2-S-(Phenylsulfonylamino)-3-(4-piperidin-4-ylbutyloxyphenyl)propionic acid hydrochloride (1-17).

1-16 (0.525 g) was treated with lithium hydroxide as described for 1-8 to give crude product that was purified by flash chromatography on silica gel eluting with $CHCl_3$(97)-MeOH(3)-HOAc(1) to provide pure acid (R_f = 0.2).
This acid was treated with HCl gas in EtOAc as described for 1-9 to provide pure 1-17.
^{1}H NMR (300 MHz, CD_3OD) δ 1.28-1.47 (6H, m), 1.50-1.70 (3H, m), 1.75 (2H, m), 1.97 (2H, d), 2.77 (1H, m), 2.95 (3H, m), 3.35 (4H, m), 3.93 (3H, m), 6.72 (2H, d), 7.02 (2H, d), 7.41 (2H, m), 7.52 (1H, m), 7.67 (2H, m).



1-4 → 1-18 → 1-19

Methyl 2-S-(2-Thienylsulfonylamino)-3-[4-(N-t-butyloxycarbonylpiperidin-4-yl)butyloxyphenyl]propionate (1-18).

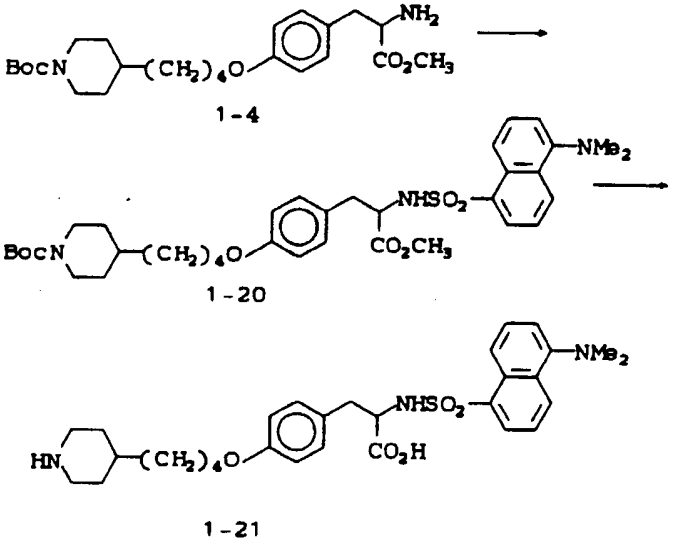
1-4 (0.304 g, 0.7 mmoles) was treated with 2-thienylsulfonyl chloride (0.155 g, 0.85 mmoles) as described for 1-8 to provide crude product. This was purified by flash chromatography on silica gel eluting with $CHCl_3$(98)-CH_3OH(2) to afford pure 1-18 as a viscous oil, R_f 0.3 [silica gel, $CHCl_3$(98)-CH_3OH(2)]
^1H NMR (300 MHz, $CDCl_3$) δ 1.10 (2H, m), 1.31 (4H, m), 1.36-1.80 (16 H, m), 2.68 (2H, bt), 3.03 (2H, d), 3.57 (3H, s), 3.91 (2H, t), 4.08 (2H, m), 4.29 (1H, m), 5.16 (1H, d), 6.78 (2H, d), 7.00 (4H, m), 7.55 (2H, dd).

2-S-(2-Thienylsulfonylamino)-3-[4-(piperidin-4-yl)butyloxyphenyl]propionic acid hydrochloride (1-19).

Treatment of 1-18 (0.22 g, 0.38 mmoles) with LiOH (0.045 g, 1.89 mmoles) as described for 1-8 provided the desired acid, which was purified by flash chromatography on silica gel eluting with $CHCl_3$(97)-CH_3OH(3)-HOAc(1).
^1H NMR (300 MHz, CD_3OD) δ 1.05 (2H, d t), 1.20-1.40 (5H, m), 1.40-1.60 (12H, m) 1.65-1.80 (5H, m), 2.65-2.82 (4H, m), 2.98 (1H, dd), 3.30 (1H, m), 3.92 (2H, t), 4.00-4.13 (5H, m), 6.75 (2H, d), 7.02 (3H, m), 7.39 (1H, d), 7.67 (1H, d).
Treatment of this acid with HCl gas as described for 1-9 provided 1-19 as a white solid after trituration.

Analysis Calcd. for $C_{22}H_{30}N_2O_5S_2$·HCl·0.5 H_2O:			
Found:	C, 51.60, C, 51.57,	H, 6.30, H, 6.20,	N, 5.47. N, 5.51.

^1H NMR (300 MHz, CD_3OD) δ 1.29-1.45 (4H, m), 1.47-1.70 (3H, m), 1.71-1.83 (2H, m), 1.91-2.00 (2H, bd), 2.79 (1H, m), 2.90-3.04 (3H, m), 3.95 (2H, t), 4.04 (1H, m), 6.76 (2H, d), 7.05 (3H, m), 7.40 (1H, m), 7.79 (1H, m).



2-S-(Dansylamino)-3-[4-(N-t-butyloxycarbonylpiperidin-4-yl)butyloxyphenyl]propionate (1-20).

1-4 (0.304 g, 0.7 mmoles) was treated with dansyl chloride (0.208 g, 0.77 mmoles) as described for 1-8 to provide crude product which was purified by flash chromatography on silica gel eluting with hexane(75)-EtOAc(25) to give pure 1-20. R_f 0.25 (silica gel eluting with hexane(75)-EtOAc(25).
^1H NMR (300 MHz, $CDCl_3$) δ 1.10 (2H, m), 1.21-1.38 (6H, m), 1.40-1.53 (11H, m), 1.60-1.80 (6H, m), 2.68 (2H, bt), 2.89 (6H, s), 3.33 (2H, s), 3.89 (2H, t), 4.05-4.19 (4H, m), 5.24 (1H, m), 6.62 (2H, d), 6.82 (2H, d), 7.18 (1H, d), 7.50 (2H, m), 8.19 (2H, t), 8.51 (1H, d).

2-S-(Dansylamino)-3-[4-(piperidin-4-yl)butyloxyphenyl]propionic acid hydrochloride (1-21).

Treatment of 1-20 (0.275 g, 0.412 mmoles) with LiOH as described for 1-8 gave the desired acid as a highly fluorescent viscous residue.

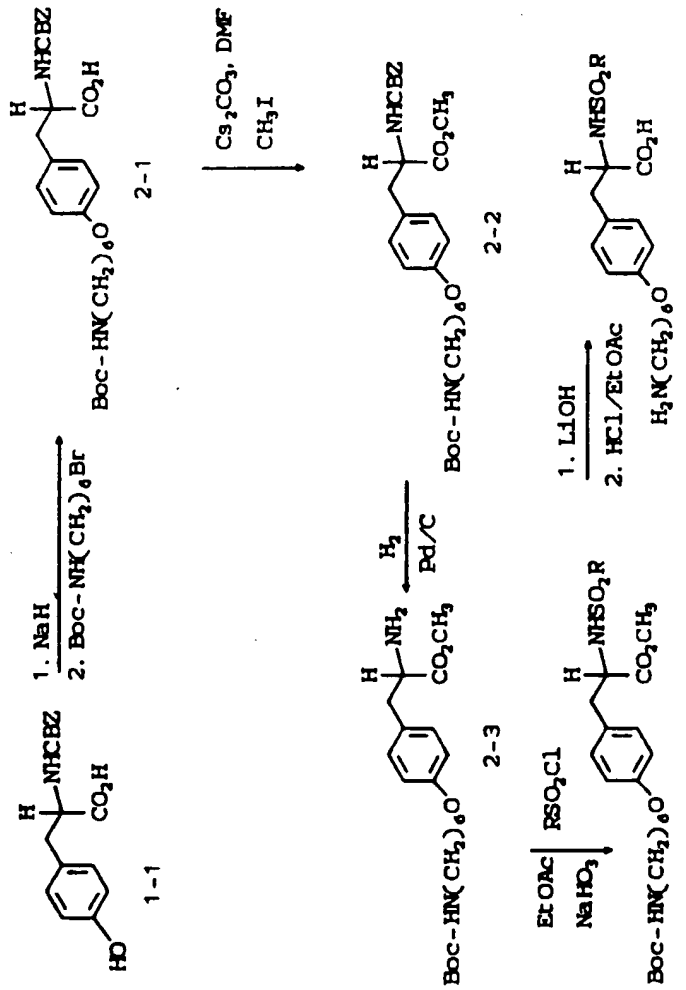
^{1}H NMR (300 MHz, CD_3OD) δ 1.09 (2H, m), 1.22-1.40 (3H, m), 1.40-1.57 (12H, m), 1.65-1.80 (3H, m), 2.60-2.80 (3H, m), 2.90 (6H, s), 3.31 (3H, m), 3.80 (2H, t), 3.90 (1H, m), 4.01-4.15 (4H, m), 6.47 (2H, d), 7.21 (1H, d), 7.42 (2H, m), 7.98 (1H, d), 8.20 (1H, d), 8.46 (1H, d).

Treatment of this acid in EtOAc with HCl gas as described for 1-9 provided 1-21 as a white solid upon ethylacetate trituration.

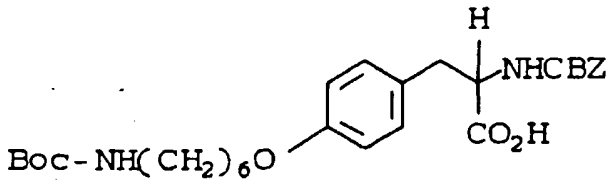
Analysis for $C_{30}H_{39}N_3O_5S \cdot 1.8\ HCl \cdot H_2O$:				
	C, 56.53;	H, 6.77;	N, 6.59;	C1, 10.01.
Found:	C, 56.48;	H, 6.66;	N, 6.36;	C1, 10.21.

^{1}H NMR (300 MHz, CD_3OD) δ 1.30-1.51 (7H, m), 1.52-1.80 (4H, m), 1.95 (2H, bt), 2.65 (1H, m), 2.95 (3H, m), 3.30-3.40 (4H, m), 3.45 (6H, s), 3.84-3.97 (3H, m), 6.45 (2H, d), 6.77 (2H, d), 7.71 (2H, m), 8.00 (1H, d), 8.16 (2H, d), 8.55 (1H, d), 8.70 (1H, d).

SCHEME 2



EXAMPLE 8



2-1

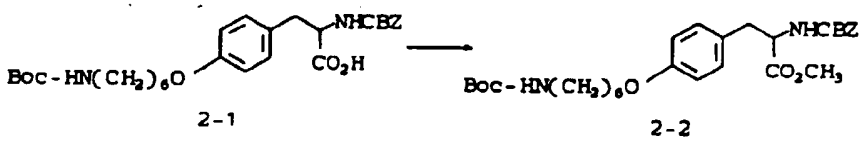
2-S-(Benzyloxycarbonylamino)-3-[4-(6-N-t-butyloxycarboxylaminohexyloxy)phenyl]propionic acid (2-1)

N-CBZ-L-tyrosine (15.0 g, 0.045 mole) was dissolved in 75 mL DMF and added at 0-10° C to a suspension of sodium hydride (2.16 g, 0.09 mole) in 25 mL DMF. The resulting suspension was stirred at 0-10° C for 1.0 hour and then 6-(t-butyloxycarbonylamino)hexyl bromide (12.6 g, 0.045 mole) in 25 mL DMF was added dropwise at 0-5° C and the clear, dark reaction mixture was stirred at room temperature overnight.

After solvent removal, the residue was taken up in EtOAc and this was made acidic with 10% $KHSO_4$ solution. The organic phase was separated, washed with brine, dried (Na_2SO_4) and the solvent removed to give an oil. This was purified by column chromatography on silica gel eluting with 98:2:1 $CHCl_3/CH_3OH$/HOAc to give pure 2-1 as a clear oil.

^1H NMR (300 MHz, CD_3OD) δ 1.45 (15H, m), 1.75(2H, m), 2.80-3.15 (6H, m), 3.91(2H, t), 4.38(1H, m), 4.95(6H, m), 6.85(2H,d), 7.06(2H,d)

EXAMPLE 9



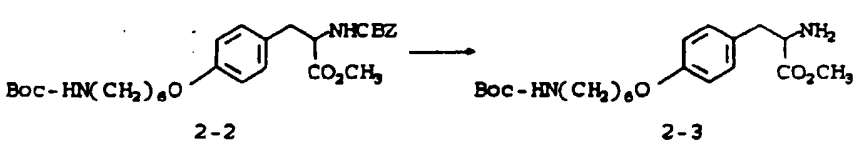
2-1 2-2

Methyl 2-S-(Benzyloxycarbonylamino)-3-[4-(6-N-t-butyloxycarbonylaminohexyloxy)phenyl]propionate (2-2)

Compound 2-1 (10.0 g, 19.43 mmole) in 75 mL DMF was treated with cesium carbonate (3.16 g, 9.72 mmole) with stirring at room temperature for 1.9 hours. Then, methyl iodide (2.76 g, 19.43 mmole) was added dropwise and the reaction mixture was stirred overnight at ambient temperature. The solvent was removed at high vacuum (30° C) and the residue was taken up in 300 mL EtOAc and washed with 2 x 40 mL protions of saturated $NaHCO_3$ solution, brine and dried (Na_2SO_4). Solvent removal provided 2-2 (8.5 g, 83%) as a clear oil.

^1H NMR (300MHz, $CDCl_3$) δ 1.25-1.53 (16H, m), 1.76 (2H, m), 2.96-3.17 (4H, m), 3.71 (3H, s), 3.90 (2H, t), 4.61 (1H, m), 5.10 (2H, m), 5.19 (1H, m), 6.88 (2H, d), 6.98 (2H, d), 7.32 (5H, m).

EXAMPLE 10



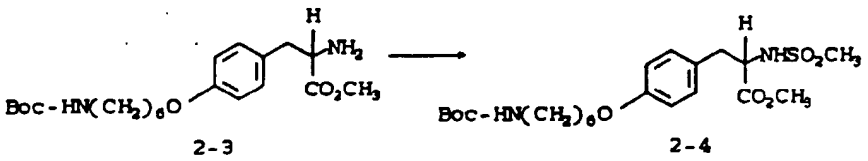
2-2 2-3

Methyl 2-S-Amino-3-[4-(6-N-t-butyloxycarbonylaminohexyloxy)phenyl]propionate (2-3)

Compound 2-2 (8.0 g, 15.1 mmole) was dissolved in 150 mL absolute ethanol and 1.0 g 10% Pd/ C was added. This suspension was hydrogenated in a Parr apparatus (50 psi) for 3.5 hours. The catalyst was then filtered off and the solvent removed on the rotary evaporator to give pure 2-3 (5.56 g) as a clear oil. R_f = 0.4 on SiO_2 with 95:5 $CHCl_3$/ CH_3OH

^1H NMR (300 MHz, $CDCl_3$) δ 1.30-1.55 (16H, m), 1.70 (2H, m), 2.80 (1H, m), 3.00-3.17 (3H, m), 3.71 (3H, s), 3.93 (2H, t), 6.82 (2H, d), 7.09 (2H,d).

EXAMPLE 11

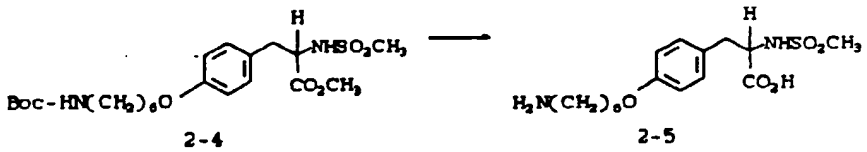


2-S-(Methylsulfonylamino)-3-[4-(6-N-t-butyloxycarbonylaminohexyloxy)phenyl]propionate (2-4)

2-3 (0.40 g, 1.01 mmole) was treated with methanesulfonyl chloride (0.116 g, 1.01 mmole) and $NaHCO_3$ (0.25 g, 3.0 mmole) as described for 1-8. The crude reaction product was purified by flash chromatography on silica gel eluting with 30% EtOAc /hexanes to give pure 2-4 (0.10g) as a clear oil.

^1H NMR (300MHz, $CDCl_3$) δ 1.36-1.56 (15H, m), 1.77 (2H, m), 2.70 (3H, s), 3.78 (3H, s), 3.92 (2H, t), 4.36 (1H, m), 4.90 (1H, d). 6.82 (2H, d), 7.09 (2H, d).

EXAMPLE 12



2-S-(Methylsulfonylamino)-3-[4-(6-aminohexyloxy)phenyl]propionic acid hydrochloride (2-5)

2-4 (0.1 g, 0.212.mmole) was treated with LiOH (0.026 g, 1.06 mmole) as described for 1-8 to provide 2-S-(methylsulfonylamino)-3-[4-(6-N-t-butyloxycarbonylaminohexyloxy)phenyl]propionic acid (0.125g) as a viscous oil.

^1H NMR (300 MHz, CD_3OD) δ 1.30-1.55 (16H, m), 1.75 (2H, m), 2.63 (3H, s), 2.85 (1H, dd), 3.0-3.13 (3H, m), 3.93 (2H, t), 4.17 (1H, m), 6.83 (2H, d), 7.20 (2H, d).

This acid was dissolved in EtOAc (20 mL) and treated with HCl gas as described for 1-9. Solvent removal provided a residue that was triturated with 30 mL Et_2O to provide pure 2-5 as a white solid (0.09 g).

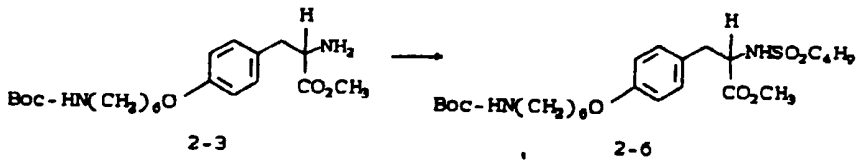
^1H NMR (300MHz, CD_3OD), δ 1.40-1.60 (4H, m), 1.60 (2H, m), 1.69 (2H, m), 2.68 (3H, s), 2.82 (1H, dd), 2.92 (2H, t), 3.10 (1H, dd), 3.30 (2H, m), 3.97 (2H, t), 4.18 (1H, m), 6.83 (2H, d), 7.19 (2H, d).

Analysis for $C_{16}H_{26}N_2O_5S.HCl.0.25\ H_2O$

Calculated: C = 48.11, H = 6.94, N = 7.01

Found: C = 48.16, H = 6.82, N = 6.98.

EXAMPLE 13



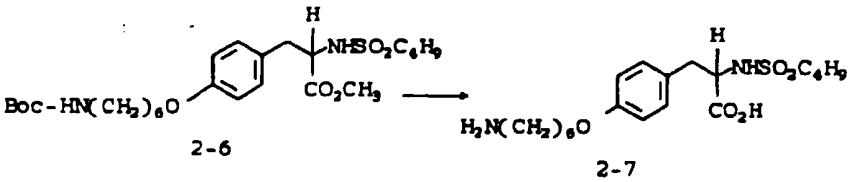
2-3 2-6

Methyl 2-S-(Butylsulfonylamino)-3-[4-(6-N-t-butyloxycarbonylaminohexyloxy)phenyl]propionate (2-6)

2-3 (0.40 g, 1.01 mmole) was treated with butylsulfonyl chloride (0.47 g, 3.03 mmole) and $NaHCO_3$ (0.50 g, 6.0 mmole) as described for 1-8. Crude reaction product was purified by flash chromatography on silica gel eluting with 30% EtOAc/hexanes to give pure 2-6 (0.22 g) as a clear oil.

^1H NMR (300MHz, $CDCl_3$) δ 0.87 (3H, t), 1.35-1.54 (18 H, m), 1.61 (2H, m), 1.77 (2H, m), 2.74 (2H, t), 2.95 (1H, dd), 3.05-3.18 (3H, M), 3.90 (2H, t), 4.32 (1H, m), 4.72 (1H, m), 6.82 (2H, d), 7.07 (2H, d).

EXAMPLE 14



2-6 2-7

2-S-(Butylsulfonylamino)-3-[4-(6-aminohexyloxy)phenyl]propionic acid hydrochloride (2-7)

2-6 (0.2 g, 0.39 mmole) was treated in THF (1)/H_2O (1)/CH_3OH(1) solution with LiOH (0.05g, 2.12 mmole) as described for 1-8 to provide 2-S-(butylsulfonylamino)-3-[4-(6-N-t-butyloxycarbonylaminohexyloxy)phenyl]propionic acid (0.235 g) as a viscous oil.

^1H NMR (300 MHz, CD_3OD) δ 0.83 (3H, t), 1.35-1.56 (16H, m) 1.76 (2H, m), 2.61 (2H, t), 2.79 (1H, ddd), 3.00-3.14 (3H, m), 3.92 (2H, t), 4.11 (1H, m), 6.82 (2H, d), 7.18 (2H, d).

This acid (0.235 g, 0.7 mmole) was dissolved in EtOAc (30 mL) and treated with HCl gas as described for 1-9. The residue was triturated with a solution of ether (40 mL)/EtOAc (10mL) to provide 2-7 (0.17g) as a white solid.

^1H NMR (300MHz, CD_3OD) δ 0.85 (3H, t), 1.24 (2H, m), 1.35-1.60 (6H, m), 1.70 (2H, m), 1.80 (2H, m), 2.66 (2H, t), 2.78 (1H, dd), 2.92 (2H, t), 3.10 (1H, dd), 3.30 (1H, m), 6.85 (2H, d), 7.20 (2H, d).

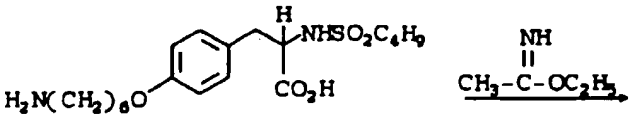
Analysis for $C_{19}H_{32}N_2O_5S.HCl$

Calculated: C = 52.22, H = 7.61, N = 6.41

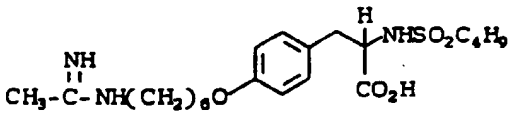
Found: C = 51.80, H = 7.61, N = 6.33.

EXAMPLE 14A

2-S-(Butylsulfonylamino)-3-[4-(6-acetamidinohexyloxy)phenyl]propionic acid (2-7a)



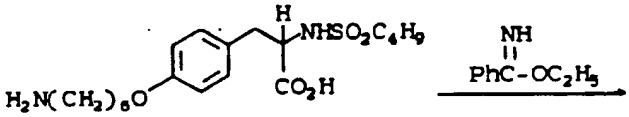
2-7



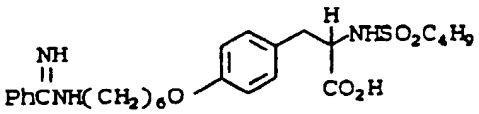
2-7a

A solution of 2-7 (1.0 g, 2.29 mmole) in THF (30 ml) is treated with ethyl acetimidate (0.2 g, 2.29 mmol) and the resulting reaction mixture is stirred at room temperature for 16 hours. The solvent is then removed and the residue is recrystallized from ethyl acetate to give pure 2-7a.

EXAMPLE 14B



2-7

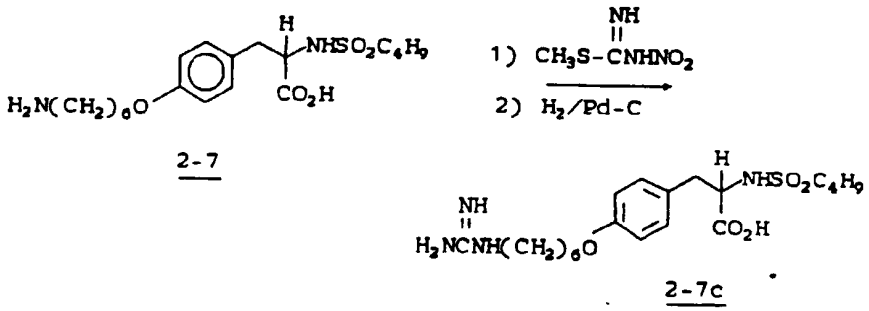


2-7b

2-S-(Butylsulfonylamino)-3-[4-(6-benzamidinohexyloxy)phenyl]propionic acid (2-7b)

A solution of 2-7 (1.0 g, 2.29 mmole) in THF (30 ml) is treated with ethyl benzimidate (0.34 g, 2.29 mmole) and the resulting solution is stirred at room temperature for 20 hrs. The solvent is removed and the residue is taken up in EtOAc, filtered and recystallized to give pure 2-7b.

EXAMPLE 14C



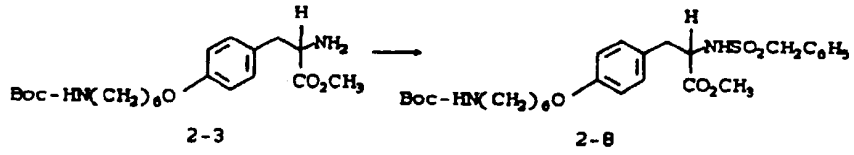
2-7c

2-S-(Butylsulfonylamino)-3-[4-(6-guanidinohexyloxyphenyl]propionic acid (2-7c)

A mixture of 2-7 (1.0 g, 2.29 mmol) and N-nitrosomethylthioguanidine (0.32 g, 2.29 mmol) is heated at 40° for 5 minutes in absolute EtOH (15 ml) and then is allowed to stand for 1 day at room temperature. The solvent is removed in vacuo and the residue is purified by flash chromatography on silica eluting with $CHCl_3$(95)-CH_3OH(5)-HOAc(2) to give the desired nitroguanidino intermediate.

This is dissolved in 10% HCl-CH_3OH (20 ml) and shaken in a Parr apparatus (50 psi) in the presence of 10% Pd-C (100 mg) at room temperature for 8 hours. The catalyst is then removed by filtration, the solvent is removed in vacuo, and the residue dissolved in 10% aqueous HCl solution and heated at reflux for 2 hours. The solvent is removed in vacuo and the residue purified by chromatography on a Dowex 1-X2 column eluting with water to give pure 2-7c.

EXAMPLE 15



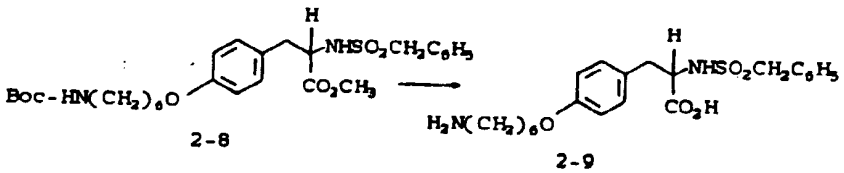
2-3 2-8

Methyl 2-S-(Benzylsulfonylamino)-3-[4-(6-N-t-butyloxycarbonylaminohexyloxy)phenyl]propionate (2-8)

2-3 (0.29 g, 0.735 mmole) was treated with benzylsulfonyl chloride (0.14 g, 0.735 mmole) and $NaHCO_3$ (0.185 g, 2.2 mmole) as described for 1-8. The crude reaction product was purified by flash chromatography on silica gel eluting with 1:1 hexanes/EtOAc to give pure 2-8 (0.27 g) as a clear oil.

^1H NMR (300 MHz, $CDCl_3$) δ 1.47-1.69 (15H, m), 1.90 (2H, m), 2.18 (2H, s), 3.08 (2H, d), 3.25 (2H, m), 3.85 (3H, s), 4.05 (2H, t), 4.19-4.20 (4H, m), 4.80 (1H, d), 6.83 (2H, d), 7.12 (2H, d), 7.47 (5H, m).

EXAMPLE 16



2-8 2-9

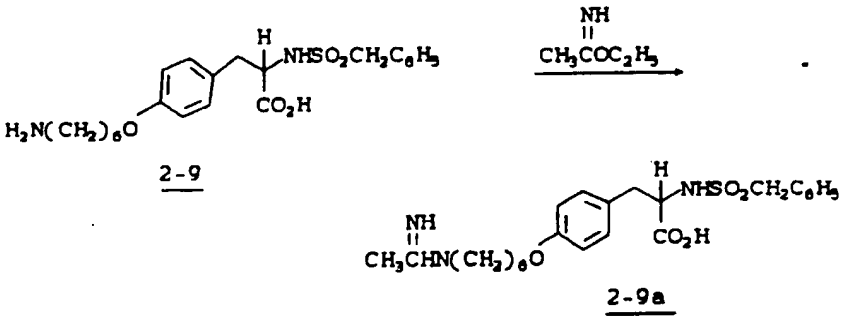
2-S-(Benzylsulfonylamino)-3-[4-(6-aminohexyloxy)phenyl]propionic acid hydrochloride (2-9)

2-8 (0.48 g, 0.875 mmole) was treated with LiOH (0.105 g, 4.37 mmole) as described for 1-8 to give 2-S-(benzyl-

sulfonylamino)-3-[4-(6-N-t-butyloxycarbonylaminohexyloxy)phenyl]propionic acid (0.4 g) as a foam.
^{1}H NMR (300 MHz, CD_3OD) δ 1.30-1.52 (15H, m), 1.72 (2H, m), 2.81 (1H, dd), 3.00 (3H, m), 3.93 (2H, m), 4.06 (2H, m), 6.81 (2H, d), 7.13 (2H, d), 7.20-7.32 (5H, m).

This acid (0.4g, 0.75 mmole) was dissolved in EtOAc (30 mL) and treated with HCl gas as described for 1-9. Crude reaction product was triturated with ether to give pure 2-9 (0.35 g) as a white solid.
^{1}H NMR (300 MHz, CD_3OD) δ 1.38-1.57 (4H, m), 1.65 (2H, m), 1.73 (2H, m), 2.71 (1H, dd), 2.89 (2H, t), 3.02 (1H, dd), 3.30 (3H, m), 3.94-4.15 (5H, m), 6.83 (2H, d), 7.15 (2H, d), 7.29 (5H, m).

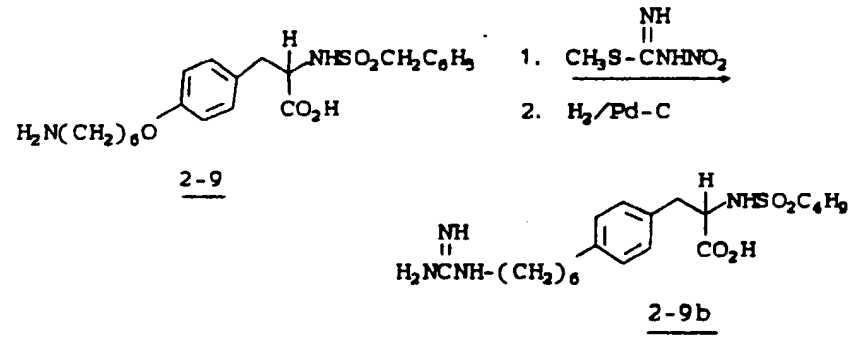
EXAMPLE 16 A



2-S-(Benzylsulfonylamino)-3-[4-(6-(acetamidinohexyloxy-phenyl)]propionic acid (2-9a)

A solution of 2-9 (1.0 g, 2.1 mmol) in THF (30 ml) is treated with ethyl acetimidate (0.18 g, 2.1 mmol) an described in Example 14A to give pure 2-9a after recrystallization from ethyl acetate.

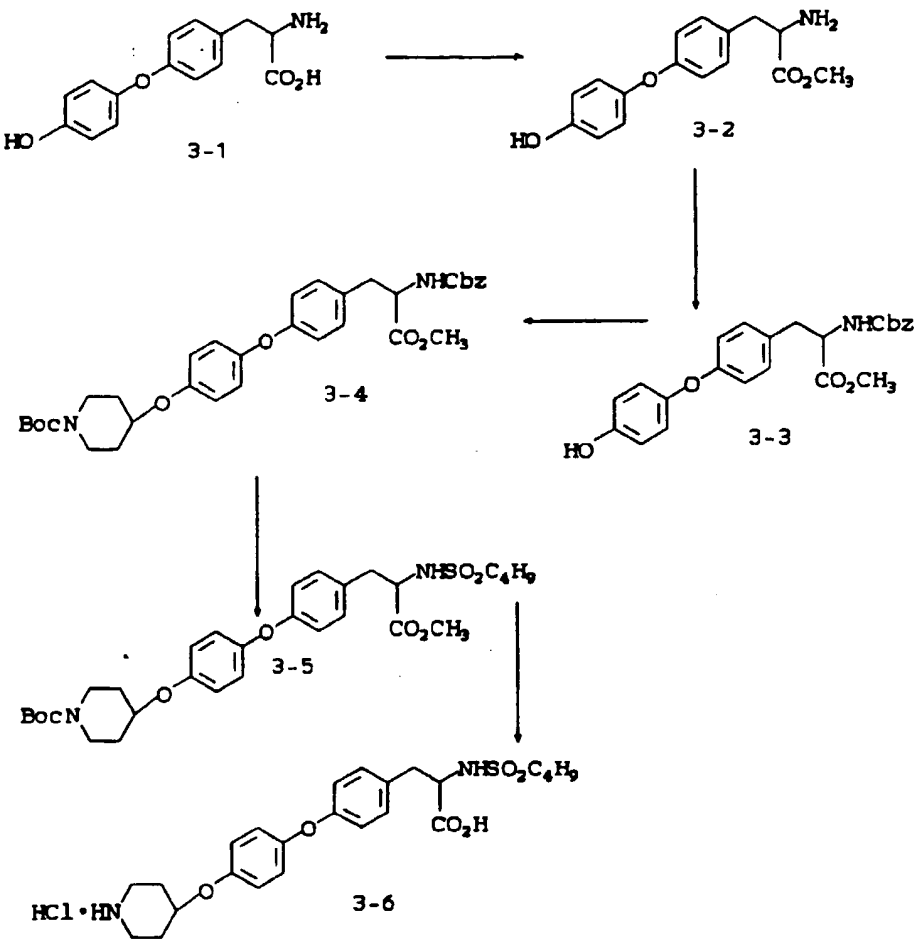
EXAMPLE 16 B



2-S-(Benzylsulfonylamino)-3-[4-(6-(guanidinohexyloxy)phenyl]propionic acid (2-9b)

A mixture of 2-9 (1.0 g, 2.1 mmol) and N-nitrosomethylthioguanidine (0.29 g, 2.1 mmol) is treated as described for Example 14C to give pure 2-9b.

SCHEME 3



Methyl 2-S-amino-3-[4-(4-hydroxyphenyl)oxyphenyl]propionate (3-2).

CH_3OH (100 ml) was cooled to 0° and treated with $SOCl_2$ (47 mmol) with stirring for 15 minutes at 0° and then 3-1 (1.5 g, 5.49 mmol) was added with stirring for 16 hours as the temperature rose to ambient.

The reaction mixture was filtered and the solvent was removed to give an oil that provided 3-2 (1.57 g) after ether washing. ^1H NMR (300 MHz, CD_3OD) δ 3.10-3.30 (2H, m), 3.81 (3H, s), 6.76-6.90 (6H, m), 7.20 (2H, d).

Methyl 2-S-(N-Benzyloxycarbonylamino)-3-[4-(4-hydroxyphenyl)oxyphenyl]propionate (3-3).

A water(1)-dioxane(1) solution (10 ml) of 3-2 (0.2 g, 0.62 mmol) was cooled to 0°C and treated with Na_2CO_3 (0.131 g, 1.23 mmole) and benzylchloroformate (0.619 mmol). After 1.5 hours of vigorous stirring, the dioxane was removed at low pressure and the residue diluted with H_2O and extracted with EtOAc. The organic extract was washed with brine, dried (Na_2SO_4) and the solvent removed to provide 3-3 as an oil.

^1H NMR (300 MHz, $CDCl_3$) δ 3.06 (2H, m), 3.75 (3H, s), 4.64 (1H, m), 5.10 (2H, m), 5.36 (1H, m), 6.83 (6H, m), 7.00 (2H, d), 7.37 (5H, bs).

Methyl-2-S-(N-Benzyloxycarbonylamino)-3-[4-(4-N-t-butyloxycarbonylpiperidin-4-yl)oxyphenyloxy]phenyl-propionate (3-4).

A benzene (40 ml) solution of 3-3 (0.5 g, 1.18 mmol) was treated with N-t-butyloxycarbonylpiperidin-4-ol (0.24 g, 1.18 mmol) and Ph_3P (0.310 g, 1.18 mmol) while stirring at room temperature with constant N_2 purging. Diethyl azodicarboxylate (1.18 mmol) was added and the resulting solution was stirred at room temperature for 16 hours.

The solvent was then removed and the residue was purified by flash chromatography on silica gel eluting with hexane(70)-EtOAc(30) to provide pure 3-4. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (9H, s), 1.80 (2H, m), 1.95 (2H, m), 3.08 (2H, m), 3.36 (2H, m), 3.76 (3H, s), 4.40 (1H, m), 4.63 (1H, m), 5.10 (1H, m), 5.25 (1H, m), 6.80-7.04 (8H, m), 7.36 (5H, bs).

Methyl 2-S-(Butylsulfonylamino)-3-[4-(4-N-t-butyloxycarbonylpiperidin-4-yl)oxyphenyloxy]phenylpropionate (3-5).

A solution of 3-4 (0.5 g, 0.082 mmol) in EtOH (40 ml) was treated with 10% Pd/C (125 mg) and this suspension hydrogenated in a Parr flask at 50 psi for 1.5 hour. The catalyst was filtered off and the solvent removed to give the desired amino ester as a clear oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (9H, s), 1.50-1.80 (8H, m), 1.91 (2H, m), 2.82 (1H, m), 3.04 (1H, m), 3.34 (2H, m), 3.76 (3H, s), 4.20 (1H, m), 7.90 (8H, m), 8.11 (2H, d).

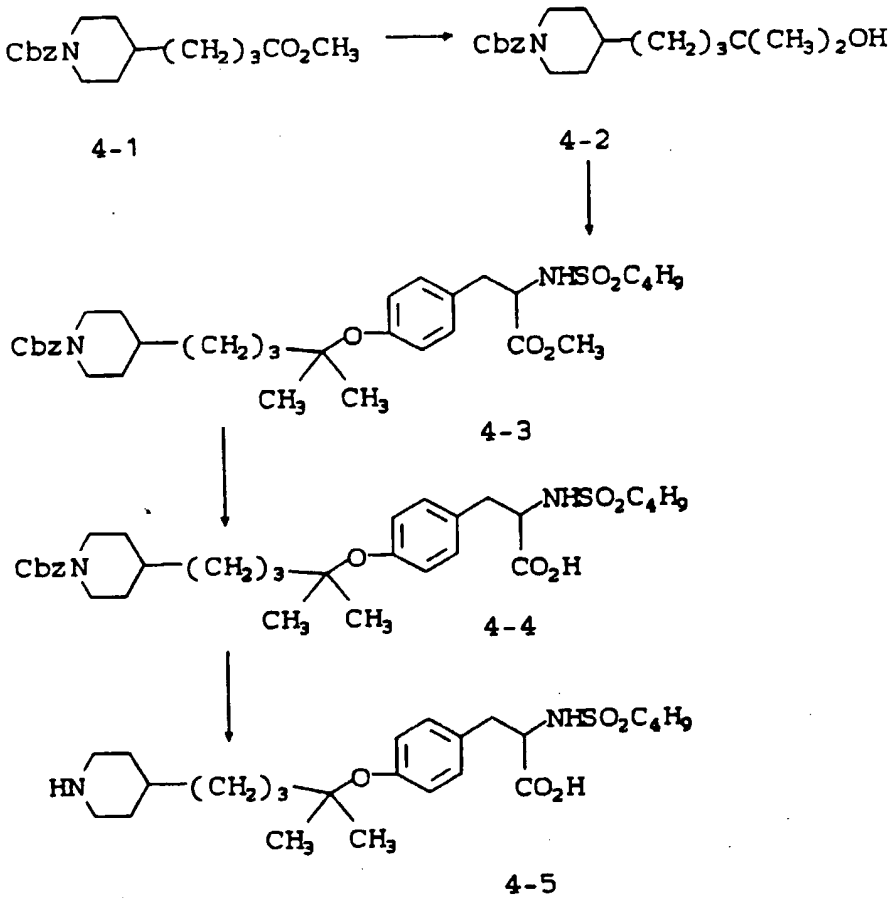
This amino ester (0.36 g, 0.77 mmol) was dissolved in EtOAc (10 ml) and treated with $NaHCO_3$ (0.386 g, 4.6 mmol) and n-butylsulfonylchloride (1.53 mmol) with heating at reflux for 48 hours. The solvent was removed and the residue purified by flash chromatography on silica gel eluting with hexane(65)-EtOAc(35) to provide pure 3-5 as an oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88-1.02 (4H, m), 1.25-1.45 (3H, m), 1.50 (9H, s), 1.51-1.80 (2H, m), 1.93 (2H, m), 2.80 (2H, m), 2.95-3.20 (2H, m), 3.21-3.40 (2H, m), 3.72 (2H, m), 3.74 (3H, s), 4.38 (2H, m), 4,80 (1H, d), 6.90 (6H, m), 7.10-7.27 (2H, m).

2-S-(Butylsulfonylamino)-3-[4-(piperidin-4-yl)oxyphenyloxy]phenylpropionic acid hydrochloride (3-6).

A solution of 3-5 (0.2 g, 0.34 mmol) in THF(1)-H_2O(1)-CH_3OH(1) was treated with LiOH (0.075 g, 1.78 mmol) at room temperature for 8 hours. The solvent was removed and the residue was acidfied with 10% $KHSO_4$ solution and this extracted several times with EtOAc. The organic extracts were combined, washed with brine, dried ($NaSO_4$) and the solvent removed to give the desired acid. R_f = 0.3 [silica gel, 97($CHCl_3$)-3(CH_3OH)-1(HOAc)].
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (3H, t), 1.20-1.30 (3H, m), 1.46 (9H, s), 1.50-2.0 (6H, m), 2.75 (2H, m), 2.97 (1H, m), 3.18 (1H, m), 3.33 (2H, m), 3.76 (2H, m), 4.35 (2H, m), 5.07 (1H, m), 6.89 (6H, m), 7.13 (2H, m).

This acid (0.15 g, 0.26 mmol) was dissolved in EtOAc and treated with HCl gas as described for 1-9 to give pure 3-6 as a white solid.
^{1}H NMR (300 MHz, CD_3OD) δ 0.89 (3H, t), 1.32 (2H, m), 1.53 (2H, m), 1.97-2.21 (4H, m), 2.75 (2H, m), 2.63 (1H, m), 3.20 (3H, m), 3.40 (2H, m), 4.14 (1H, m), 6.82-7.05 (6H, m), 7.23 (2H, m).

SCHEME 4



4[4-(N-Benzyloxycarbonylpiperidin-4-yl)-2-methyl]pentan-2-ol(4-2).

Methyl 4-(N-Benzyloxycarbonylpiperidin-4-yl)butanoate (4-1) (10.07 g, 0.032 mol) in THF (200 ml) was cooled to 0°C and treated with CH_3MgI (0.095 mol) for 3.0 hours. The reaction mixture was poured into ice, acidified with 10% $KHSO_4$ and extracted with 3 portions of EtOAc. The combined organic extract was washed with brine, dried ($MgSO_4$) and the solvent removed. The residue was purified by flash chromatography on silica gel eluting with hexane(7)-EtOAc (3) to give pure 4-2. R_f = 0.3 (silica gel, hexane (7)-EtOAc(3).

Methyl 2-S-(Butylsulfonylamino)-3-[4-(N-Benzyloxycarbonylpiperidin-4-yl)-2,2-dimethyl]butyloxyphenylpropionate (4-3).

N-n-Butylsulfonyl-L-tyrosine methyl ester (7.21 g, 0.023 mole) was dissolved in a mixture of 4-2(1.0g), CH_2Cl_2 (30 ml) and benzene (250 ml). Triphenylphosphine (5.97 g, 0.023 mole) was added and after purging with N_2, diethyl

azodicarboxylate (3.6 ml, 0.023 mole) was added at room temperature as the reaction mixture turned red-orange in color. Reaction mixture stirred at room temperature for 7 days. Solvent was removed and the residue was purified by flash chromatography on silica gel eluting with hexane(60)-EtOAc(40) to give pure 4-3.
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (6H, t), 1.10-1.40 (12H, m), 1.43-1.78 (8H, m), 2.70-2.82 (4H, m), 2.95-3.10 (3H, m), 3.75 (3H, s), 4.18 (2H, m), 4.32 (1H, m), 5.13 (2H, s), 6.88 (2H, d), 7.06 (2H, d), 7.38 (5H, m).

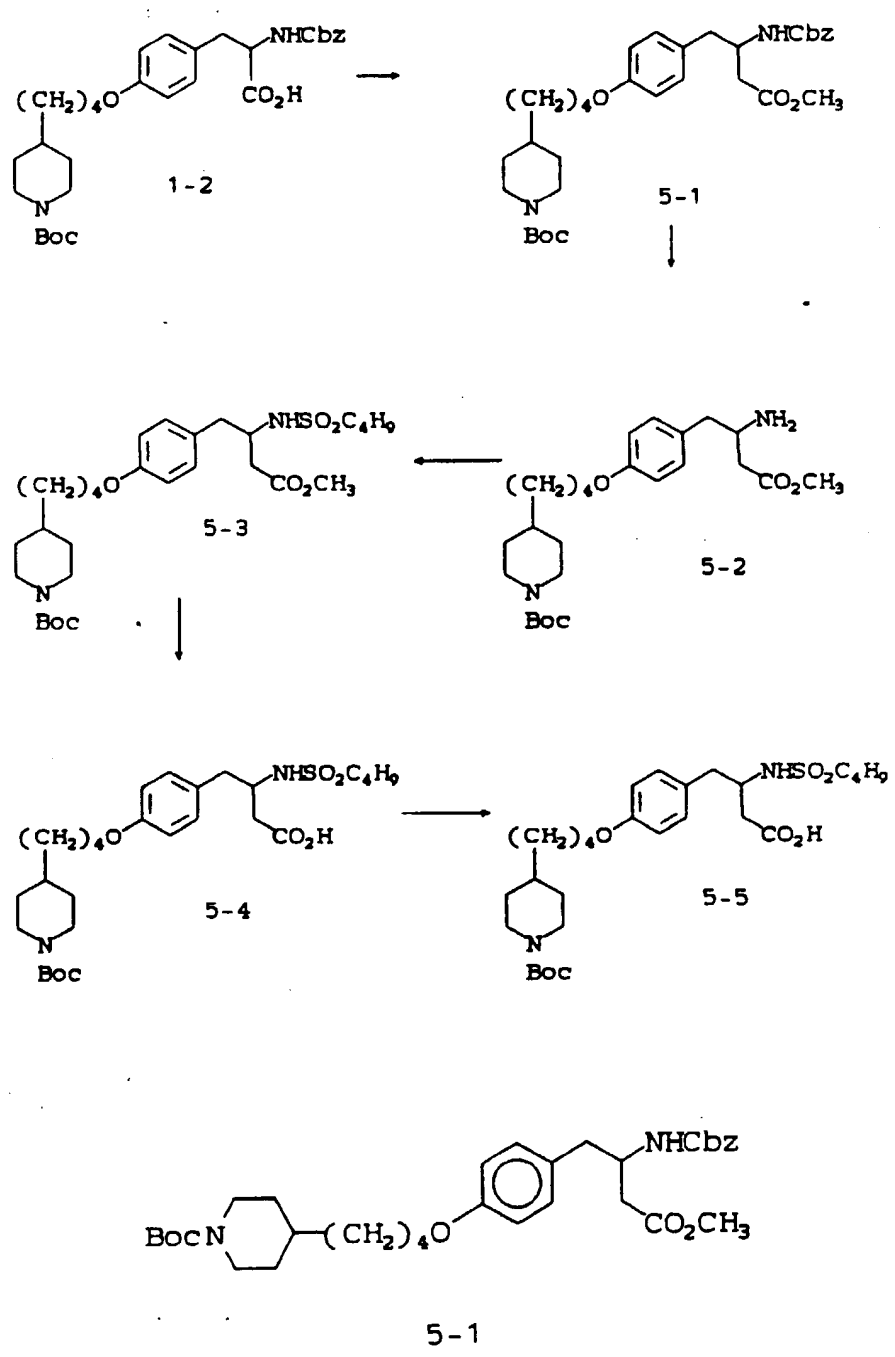
2-S-(Butylsulfonylamino)-3-[4-(N-Benzyloxycarbonylpiperidin-4-yl)-2,2-dimethyl]butyloxyphenylpropionic acid (4-4).

Dissolved 4-3 (0.64 g, 0.001 mole) in THF/H_2O/CH_3OH mixture and treated with LiOH (0.26 g, 0.0062 mole) at room temperature for 8 hours. Solvent removal, acidification ($KHSO_4$ solution) and EtOAc extraction provided crude 4-4 which was purified by flash chromatography on silica gel eluting with $CHCl_3$(97)-CH_3OH(3)-HOAc(1) to give pure 4-4.
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (6H, s), 1.05-1.50 (13H, m), 1.55-1.80 (5H, m), 2.77 (4H, m), 3.04 (2H, m), 4.10 (2H, bd), 4.17 (1H, m), 4.85 (1H, d), 5.14 (2H, s), 6.88 (2H, d), 7.13 (2H, d), 7.39 (5H, m).

2-S-(Butylsulfonylamino)-3-[4-(piperidin-4-yl)-2,2-dimethyl]butyloxyphenylpropionic acid (4-5).

To ammonium formate (0.23 g, 3.65 mmol) in CH_3OH (5 ml) was added 4-4 (0.22 g, 3.65 mmole) in 10 ml CH_3OH and then 10% Pd/C (100 mg) was added at room temperature. After 15 minutes the reaction mixture was passed thru a Solka Floc pad and the solvent removed. This residue was purified by flash chromatography on silica gel eluting with EtOH(9)-H_2O(1)-NH_4OH(1) to give pure 4-5.
^{1}H NMR (300 MHz, CD_3OD) δ 0.88 (6H, s), 1.15-1.40 (12H, m), 1.42-1.70 (7H, m) 1.90 (2H, d), 2.78-3.00 (6H, m), 3.06 (1H, dd), 3.35 (3H, m), 3.93 (1H, m), 6.86 (2H, d), 7.20 (2H, d).

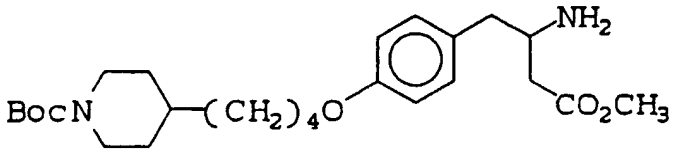
SCHEME 5



Methyl 3-S-(Benzyloxycarbonylamino)-4-[4-(N-t-butyloxycarbonylpiperidin-4-yl)butyloxyphenyl]butyrate (5-1).

A solution of compound 1-2 (1.0 g, 1.8 mmole) and N-methylmorpholine (0.21 mL, 1.9 mmole) in EtOAc (10 mL)

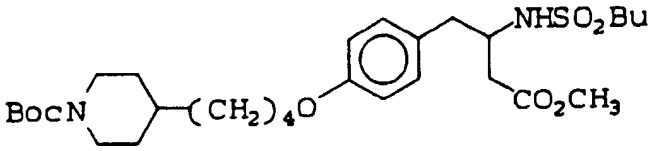
was stirred at -15°C and treated with isobutyl chloroformate (0.24 mL, 1.8 mmole). After 15 minutes the heterogeneous mixture was treated portion-wise with an ethereal solution of diazomethane (0.5M:10 mL, 5.0 mmole), followed by continued stirring at 0° for 1.0 hour. The reaction mixture was then purged with argon for 10 minutes to remove excess diazomethane. The organic phase was washed with 2 x 5 mL portions of H_2O, brine, dried ($MgSO_4$), and evaporated. The residue was then dissolved in CH_3OH (15 mL) and treated sequentially with triethylamine (0.7 mL, 5.0 mmole) and AgO_2CPh (110 mg, 0.5 mmole) while stirring at ambient temperature to effect vigorous gas evolution. After 30 minutes the solvent was evaporated and then the crude reaction product purified by flash chromatography on silica gel eluting with 4:1 hexane/EtOAc to give 5-1 (0.52 g) as an oil. TLC R_f = 0.23 (30% EtOAc/hexane)



5-2

Methyl 3-S-Amino-4-[4-(N-t-butyloxycarbonylpiperidin-4-yl)butyloxyphenyl]butyrate (5-2).

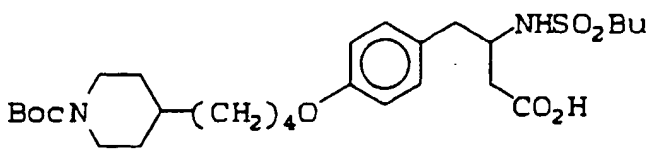
To 5-1 (0.52 g, 0.9 mmole) dissolved in absolute ethanol (20 mL) was added 10% Pd/C (0.25 g) and the resulting suspension was hydrogenated under balloon pressure for 12 hours. The catalyst was then filtered off and the solvent was removed in vacuo to give 5-2 (0.35 g) as an oil.
TLC R_f = 0.15 (9:1:1 $CH_2Cl_2/CH_3OH/AcOH$).



5-3

Methyl 3-S-(Butylsulfonylamino)-4-[4-N-t-butyloxycarbonylpiperidin-4-yl)butyloxyphenyl]butyrate (5-3).

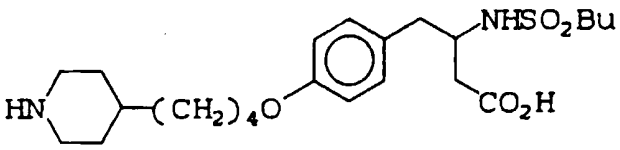
To 5-2 (0.36 g, 0.8 mmole), triethylamine (170 µL, 1.2 mmole), 4-dimethylaminopyridine (12 mg, 0.1 mmole), and THF (5 mL) at 0°C was added n-butylsulfonyl chloride (130 µL, 1.0 mmole) with stirring. The cooling bath was removed and stirring was continued for 6 hours. The reaction mixture was diluted with 10 mL of EtOAc and then washed with 2x5 mL H_2O, brine, dried ($MgSO_4$), and concentrated. The crude reaction product was purified by flash chromatography on silica gel eluting with 4:1 hexane/EtOAc to give 5-3 (180 mg) as an oil.
^1H NMR (300 MHz, $CDCl_3$) δ 1.12 (2H, m), 1.25-1.83 (13H, m), 1.29 (3H, t), 1.47 (9H, s), 2.68 (6H, m), 2.87 (2H, d), 3.73 (3H, s), 3.93 (2H, t), 4.08 (1H, m), 4.72 (1H, d), 6.87 (2H, d), 7.12 (2H, d).



5-4

3-S-(Butylsulfonylamino)-4-[4-N-t-butyloxycarbonylpiperidin-4-yl)butyloxyphenyl]butanoic acid (5-4).

Compound 5-3 (175 mg, 0.33 mmole) in CH_3OH (4.0 mL) was treated with IN NaOH (1.0 mL, 1.0 mmole) followed by continued stirring at ambient temperature for 20 hours. The reaction mixture was diluted with 15 mL EtOAc and then washed with 10 mL 5% $KHSO_4$ and brine, dried ($MgSO_4$), and concentrated to give 5-4 (160 mg) as an oil. TLC R_f = 0.31 (9:0.5:0.5 $CH_2Cl_2/CH_3OH/AcOH$).

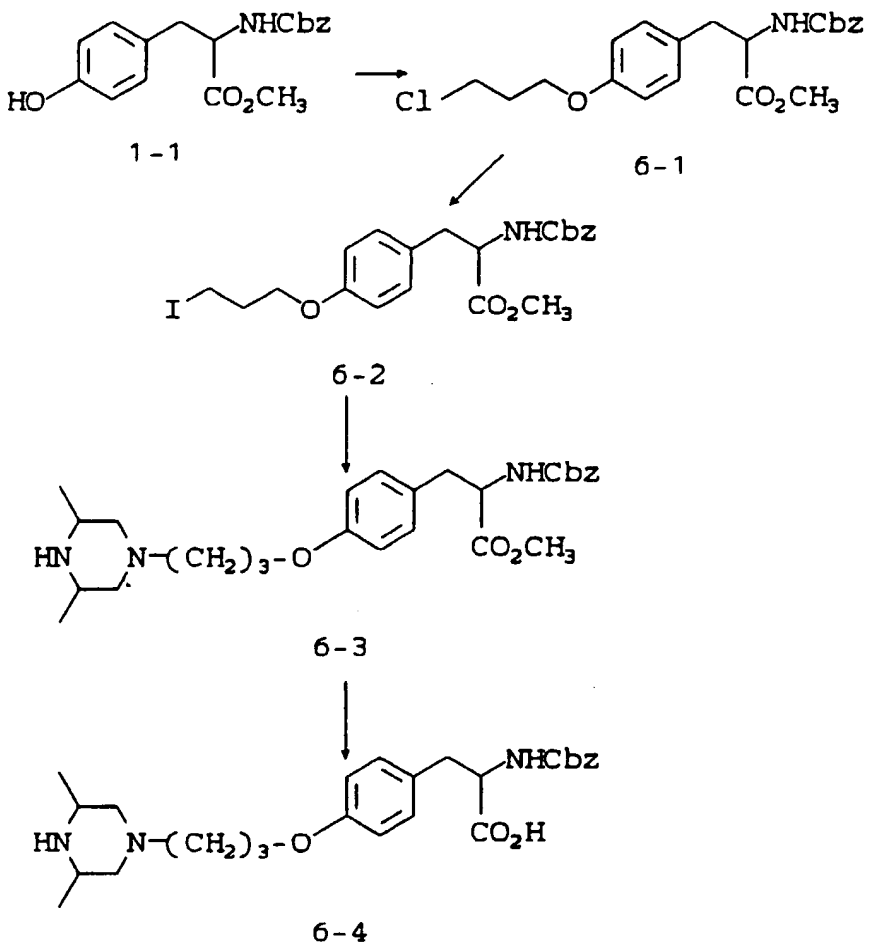


5-5

3-S-(Butylsulfonylamino)-4-[4-piperidin-4-yl)butyloxyphenyl]butanoic acid (5-5)

To a stirred solution, of compound 5-4 (160 mg, 0.30 mmole), CH_2Cl_2 (2.0 mL), and anisole (100 µL) at 0°C was added CF_3CO_2H (1.0 mL). After 1.5 hours at 0°C the solvents were evaporated and the crude reaction product purified by flash chromatography on silica gel eluting with 10:0.8:0.8 ethanol/H_2O/conc. NH_4OH to give 5-5 (42 mg) as a solid. ^1H NMR (300 MHz, D_2O/CF_3CO_2D) δ 0.82 (3H, t), 1.10-1.70 (11H, m), 1.80 (m, 2H), 1.98 (m, 2H), 2.48 (2H, t), 2.72 (3H, m), 3.00 (3H, m), 3.43 (2H, m), 3.96 (1H, m), 4.10 (2H, t), 7.01 (2H, d), 7.32 (2H, d).

SCHEME 6



Methyl 2-S-(N-Benzyloxycarbonylamino)-3-[4-(3-chloropropyloxyphenyl)propionate (6-1).

Treatment of a DMF solution of 1-1 (0.95 g, 2.9 mmol) and 3-chloro-1-tosyloxypropane (0.84 g, 3.19 mmol) with cesium carbonate (0.47 g, 1.45 mmole) gave a solution that was stirred at room temperature overnight. The reaction mixture was then diluted with H_2O and extracted with ether. The ether extract was washed with brine, dried (Na_2SO_4) and the solvent removed to give an oily residue. This was purified by flash chromatography on silica gel eluting with EtOAc(5)-hexane(95) to afford 6-1 as a clear oil. R_f 0.5 (silica gel eluting with EtOAc(30)-hexane(70).

Methyl 2-S-(Benzyloxycarbonylamino)-3-[4-(3-iodopropyloxyphenyl)propionate (6-2).

A solution of 6-1 (0.6 g, 1.5 mmol) in acetone was treated with sodium iodide (1.1 g, 7.5 mmol) and the resulting solution was heated at reflux for 16 hours. The reaction mixture was then diluted with ether, washed with water, brine and dried (Na_2SO_4). Solvent removal gave an oil that was purified by flash chromatography on silica gel eluting with hexane(90)-EtOAc(10) to give 6-2 as a clear oil.

^1H NMR (300 MHz, $CDCl_3$) δ 1.85-2.08 (4H, m), 3.04 (2H, m), 3.26 (2H, t), 3.71 (3H, s), 3.95 (2H, t), 4.60 (1H, m),

5.00-5.21 (3H, m), 6.78 (2H, d), 6.99 (2H, d), 7.33 (5H, m).

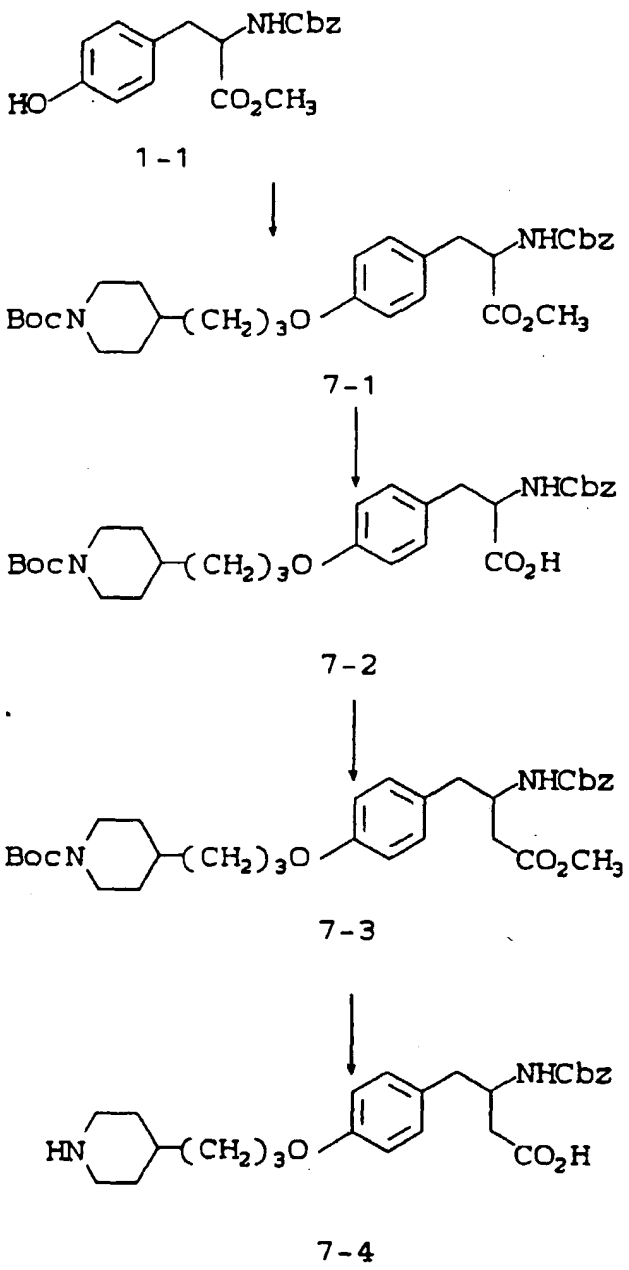
Methyl 2-S-(N-Benyzloxycarbonylamino)-3-[4-(2,6-dimethylpiperazin-4-yl)propyloxyphenyl]propionate (6-3).

A solution of 6-2 (0.1 g, 0.2 mmol) and 2,6-dimethylpiperazine(0.068 g, 0.6 mmol) in 1 ml THF was stirred at room temperature for 20 hours. The solvents were removed at low pressure to provide 6-3 as a clear oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (4H, d), 1.82 (3H, m), 2.65 (2H, m), 2.79 (2H, m), 3.05 (1H, m), 3.18 (2H, bd), 3.60 (1H, m), 3.72 (3H, s), 3.96 (2H, m), 4.62 (1H, m), 5.10 (2H, s), 5.21 (1H, m), 6.79 (2H, d), 7.00 (2H, d), 7.35 (5H, bs).

2-(N-Benzyloxycarbonylamino)-3-[4-(2,6-dimethylpiperazin-4-yl)propyloxyphenyl]propionic acid (6-4).

6-3 (0.090 g, 0.2 mmol) in methanol was treated with IN NaOH (0.7 ml) at room temperature for 16 hours. The solvent was removed to give crude acid which was purified by flash chromatography on silica gel eluting with isopropanol(10)-NH_4OH(1)-H_2O(1) to provide pure 6-4, R_f 0.25.
^{1}H NMR (300 MHz, CD_3OD) δ 1.65-1.85 (4H, m), 2.60-2.70 (2H, m), 2.80-2.95 (6H, m), 3.11 (8H, m), 3.52 (2H, m), 3.65-3.75 (2H, m), 3.82 (2H, t), 4.17 (1H, m), 4.70 (2H, s), 4.85 (2H, m), 6.63 (2H, d), 6.92 (2H, d), 7.10 (5H, bs).

SCHEME 7



Methyl 2-S-(N-Benzyloxycarbonylamino)-3-[4-(N-t-butyloxycarbonylpiperidin-4-yl)propyloxyphenyl]propionate (7-1).

A solution of 1-1 (4.0 g, 2.6 mmol) and 3-(N-Boc-piperidin-4-yl)propyl iodide (1.1 g, 3.3 mmol) in 40 ml DMF was treated with cesium carbonate (0.4 g, 1.35 mmol) and the resulting solution was stirred at room temperature for 20 hours. The solvent was removed and the residue was taken up in EtOAc, washed with water, brine and dried (Na_2SO_4). Solvent removal provided a residue that was purified by flash chromatography on silica gel eluting with 4:1 hexane (80)-EtOAc(20) to give pure 7-1 as a clear oil.

^1H NMR (300 MHz, $CDCl_3$) δ 1.10 (2H, m), 1.37-1.45 (11H, m), 1.65-1.82 (4H, m), 2.68 (2H, m), 3.03 (2H, m), 3.71

(3H, s), 3.90 (2H, t), 4.08 (2H, bd), 4.61 (1H, m), 5.10 (1H, s), 5.18 (1H, m), 6.79 (2H, d), 7.00 (2H, d), 7.35 (5H, bs).

2-(S)-(N-Benzyloxycarbonylamino)-3-[4-(N-t-butyloxycarbonylpiperidin-4-yl)propyloxyphenyl]propionic acid (7-2).

7-1 (0.5 g, 0.9 mmol) in methanol (12 ml) was treated with 1N NaOH (3 ml) at room temperature for 16 hours. The solvent was then removed and the residue acidified with 5% $KHSO_4$ solution. This was extracted with EtOAc several times and the combined organic extracts were washed with brine and dried (Na_2SO_4). Solvent removal gave 7-2 as a clear oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (2H, m), 1.37-1.52 (12H, m), 1.62-1.85 (5H, m), 2.66 (2H, t), 3.10 (2H, m), 4.89 (2H, t), 4.10 (4H, m), 4.62 (1H, m), 5.09 (1H, s), 5.19 (1H, m), 6.79 (2H, d) 7.03 (2H, d), 7.34 (5H, bs).

Methyl 3-S-(N-Benzyoxycarbonylamino)-4-[4-(N-t-butyloxycarbonylpiperidin-4-yl)propyloxyphenyl)butanoate (7-3).

To a stirred solution of 7-2 (1.6 g, 2.9 mmol) in EtOAc at -15°C was added isobutylchloroformate (2.9 mmol) and N-methylmorpholine (2.9 mmol) and the resulting solution was stirred for 0.5 hours at -15°. Then, diazomethane (5.0 mmol in Et_2O) was added and the reaction mixture was stirred at 0° for 20 minutes. The reaction mixture was purged with argon, diluted with EtOAc and washed with water. The organic phase was dried ($MgSO_4$) and the solvent removed to provide the desired diazoketone.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (2H, m), 1.35-1.50 (12H, m), 1.55-1.85 (6H, m), 2.68 (2H, bt), 2.95 (2H, d), 3.90 (2H, t), 4.09 (3H, m), 4.42 (1H, m), 5.06 (1H, m), 5.20 (1H, m), 5.35 (1H, m), 6.80 (2H, d), 7.06 (2H, d), 7.35 (5H, bs).

This diazoketone (1.63 g, 2.9 mmol) was dissolved in CH_3OH (20 ml) and treated at room temperature with a CH_3OH solution (5 ml) of silver benzoate (0.22 mg, 0.96 mmoles) and triethylamine (1.25 ml). After a few minutes the reaction became black with gas evolution apparent. After 0.5 hours the solvent was removed and the residue was purified by flash chromatography on silica gel eluting with 4:1 hexane(80) EtOAc(20) to give 7-3 as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (2H, m), 1.37-1.47 (12H, m), 1.60 (2H, s), 1.65-1.83 (4H, m), 2.49 (2H, m), 2.62-2.91 (4H, m), 3.67 (3H, s), 3.90 (2H, t), 4.03-4.20 (4H, m), 5.08 (2H, s), 5.24 (1H, m), 6.79 (2H, d), 7.05 (2H, d), 7.32 (5H, bs).

3-S-(N-Benzyloxycarbonylamino)-4-[4-(piperidin-4-yl)propyloxyphenyl]butanoic acid (7-4).

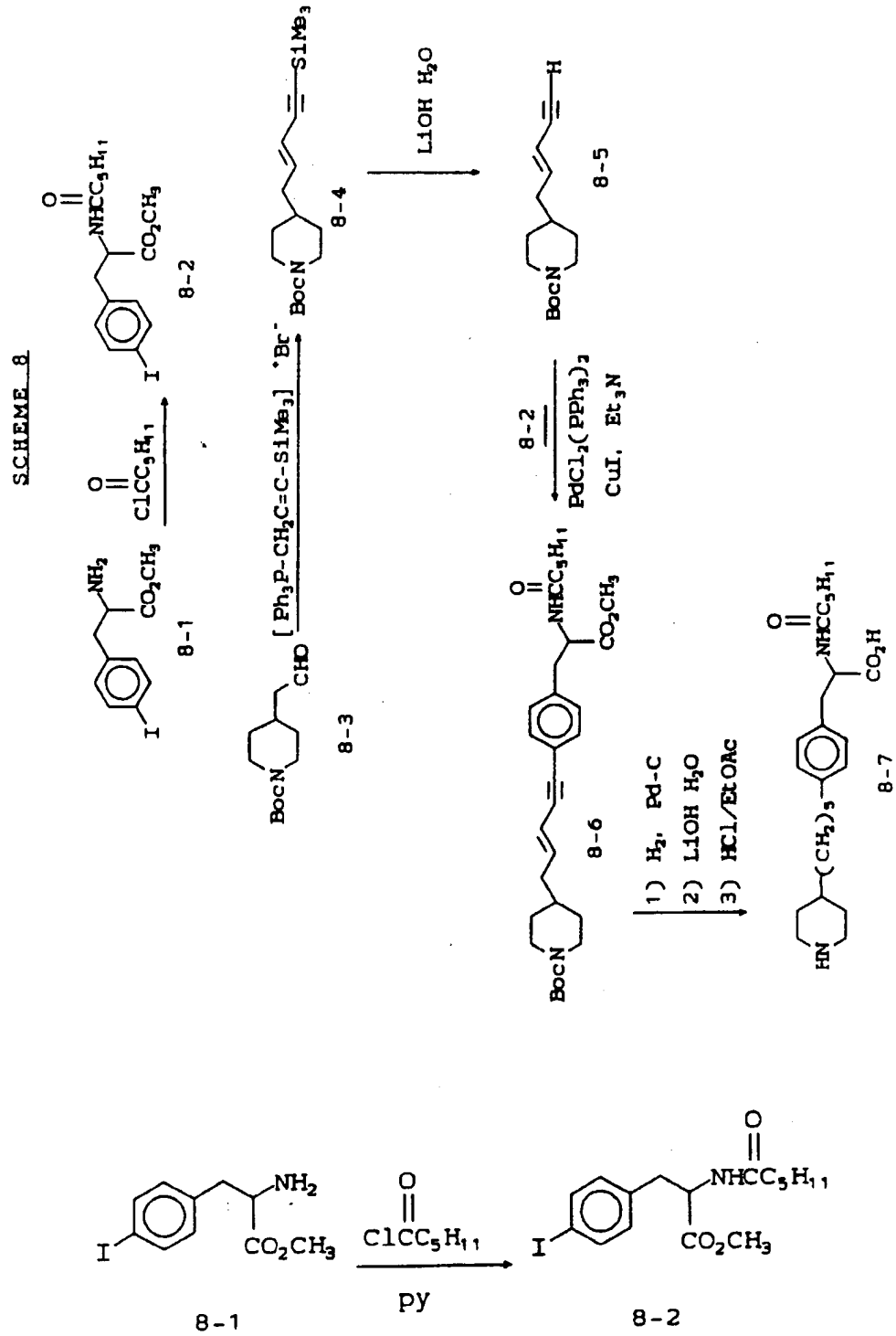
A solution of 7-3 (0.3 g, 0.53 mol) was treated with 1N NaOH (1.7 ml) and the resulting mixture was stirred at room temperature for 16 hours. The solvent was removed and the residue acidified with 5% aq $KHSO_4$ solvent and this was extracted several times with EtOAc. The combined organics were washed with brine, dried ($NaSO_4$) and the solvent removed to give the desired acid.

^{1}H NMR (300 MHz, CD_3OD) δ 1.10 (2H, m), 1.40-1.52 (12, m), 1.65-1.84 (6H, m), 2.54-2.93 (8H, m), 3.92 (2H, t), 4.05-4.12 (3H, m), 5.10 (2H, s), 6.71 (2H, d), 7.08 (2H, d), 7.35 (5H, m).

This acid was dissolved in CH_2Cl_2 (4 ml) and anisole (0.41 mmole) was added, followed at 0° with trifluoroacetic acid (2 ml). After 2.5 hours stirring at 0°, the solvents were removed and the residue purified by flash chromatography on silica gel eluting with EtOH(10)-NH_4OH(1)-H_2O(1) to give pure 7-4 as a white solid.

^{1}H NMR (300 MHz, CD_3OD) δ 1.3-1.5 (4H, m), 1.6 (1H, m), 1.75-1.85 (2H, m), 1.95 (2H, d), 2.54 (2H, m), 2.72 (2H, m), 2.93 (2H, t), 3.32 (6H, m), 3.92 (2H, t), 4.11 (1H, m), 4.95 (2H, m), 6.75 (2H, d), 7.05 (2H, d), 7.25 (5H, m).

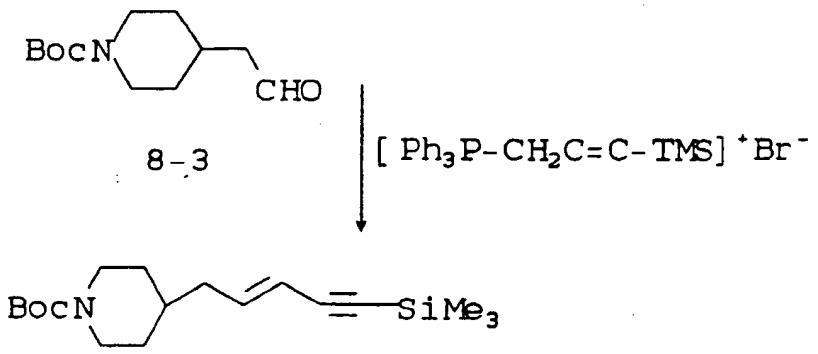
SCHEME 8



Methyl 2-S-(Hexanoylamino)-3-(4-iodophenyl)propionate (8-2)

A suspension of 8-1 (1.01 g, 2.96 mmoles) in 20 ml $CHCl_2$ was cooled to 0° and pyridine (1.43 ml, 17.7 mmoles) was added followed by hexanoylchloride (1.25 ml, 8.88 mmoles). After 20 minutes all 8-1 was consumed. Water (25

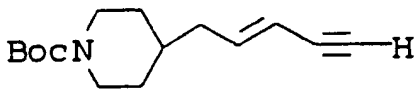
ml) was then added carefully and this mixture was extracted with EtOAc (150 ml). The separated organic phase was washed with 10% $KHSO_4$, brine, dried (Na_2SO_4) and the solvent was removed to give a white solid. This was purified by flash chromatography on silica gel eluting with 5% $Et_2O/CHCl_3$ to give pure 8-2 (1.07 g) as a white solid.
^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t), 1.27 (4H, m), 1.60 (2H, m), 2.09 (2H, t), 3.05 (2H, m), 3.75 (3H, s), 4.88 (1H, m), 5.93 (1H, m), 6.83 (2H, d), 7.60 (2H, d).



8-4

5-(N-t-Butyloxycarbonylpiperidin-4-yl)-1-trimethyl-1-silylpent-3-ene-1-yne (8-4).

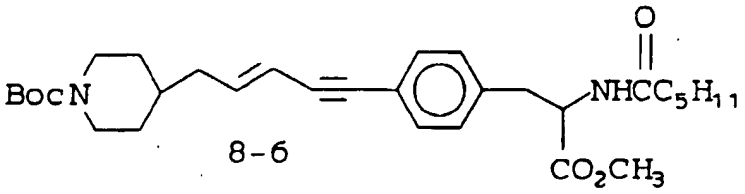
A suspension of 3-trimethylsilyl-2-propynyl)triphenyl phosphonium bromide (3.0 g, 6.62 mmoles) (Aldrich) in 50 ml THF was cooled to -78° and treated with n-BuLi (6.62 mmoles) dropwise. The resulting solution was allowed to warm to -40° and was then stirred for 0.5 hours to give a deep red solution. After cooling to -78°C the reaction mixture was treated with 8-3 (1.07 g, 4,73 mmoles) in 15 ml THF and was allowed to warm to 0° with stirring for 1 hour. The reaction was quenched with 50 ml H_2O and this was extracted with EtOAc (200 ml). The organic phase was separated, dried (Na_2SO_4) and stripped to provide as residue that was purified by flash chromatography on silica gel eluting with 10% EtOAc/hexane to provide pure 8-4, (2.02 g), $R_f = 0.3$.
^1H NMR (300 MHz, $CDCl_3$) δ 0.10 (9H, s), 0.70-1.10 (4H, m), 1.10-1.40 (13H, m), 1.40-1.60 (3H, m), 1.83 38H, m), 2.40-2.60 (3H, m), 3.85 (3H, m), 5.35 (1H, t), 6.00 (1H, m).



8-5

5-(N-t-Butyloxycarbonylpiperidin-4-yl)pent-3-en-1-yne (8-5)

A solution of 8-4 (0.815 g, 2.54 mmoles) in 60 ml THF was treated with 12 ml H_2O and lithium hydroxide hydrate (0.96 g, 2.28 mmoles). The reaction mixture was stirred at room temperature for 6 hours during which time the color became dark orange. The reaction mixture was then diluted with Et_2O (75 ml) and the aqueous phase was separated and washed with 3x75 ml Et_2O. The combined organic extacts were washed with brine, dried and stripped. The resulting residue was purified by flash chromatography on silica gel eluting with 10% EtOAc/hexanes to give 0.63 g pure 8-5.
^1H NMR (300 MHz, $CDCl_3$) δ 1.0-1.25 (3H, m), 1.25-1.60 (11H, m), 1.60-1.75 (3H, m), 2.06 (2H, t), 2.30 (1H, t), 2.60-2.78 (2H, m), 4.07 (2H, m), 5.51 (1H, m), 6.22 (1H, m).



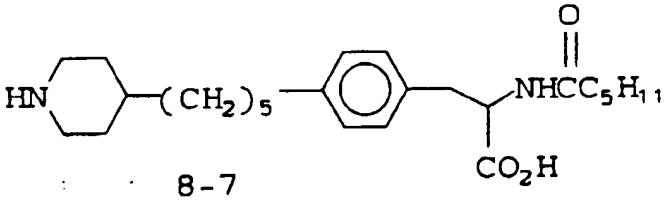
8-6

Methyl 2-S-(Hexanoylamino)-3-[4-(5-N-t-butyloxycarbonylpiperidin-4-yl)pent-3-ene-1-ynephenyl]propionate (8-6).

A solution of 8-5 (0. 3 g, 1.2 mmoles) and 8-2 (0.58 g, 1.4 mmoles) in diethylamine (6 ml) was purged with N_2 and bis-triphenylphosphine palladium chloride (0.049 g, 0.07 mmoles) was added followed by cuprous iodide (7 mg, 0.035 mmoles) and the suspension was purged again. After several minutes the reaction mixture became homogeneous and this solution was stirred for 16 hours at room temperature.

The solvent was removed at high vacuum and the residue was dissolved in pH 7 buffer and extracted with Et_2O. The organic extract was washed with 10% $KHSO_4$, brine, then dried (Na_2SO_4) and stripped. The residue was purified by flash chromatography on silica gel eluting with 20% EtOAc/hexanes to give 0.28 g pure 8-6. R_f = 0.3 (20% EtOAc, hexanes).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (3H, m), 1.05-1.40 (9H, m), 1.52 (6H, s), 1.58-1.75 (4H, m), 2.07 (2H, m), 1.70 (2H, m), 3.14 (2H, m), 3.75 (2H, m), 4.10 (2H, m), 4.89 (1H, m), 5.70 (1H, m), 5.94 (1H, m), 6.18 (1H, m), 7.03 (2H, m), 7.38 (2H, m).



8-7

2-S-(Hexanoylamino)-3-[4-(5-Piperidin-4-yl)pentylphenyl]propionic acid (8-7)

8-6 (0.275 g, 0.52 mmoles) was dissolved in EtOH and 2 ml of H_2O was added along with 5 drops of HOAc. Pd-C (100 mg) was added and the resulting suspension was hydrogenated on a Paar shaker (50 psi) for 4 hours. The reaction mixture was filtered through Solka-Floc and the resulting solvent was removed. The resulting residue was purified by flash chromatography on silica gel eluting with 35% EtOAc/hexanes to give 0.22 g of methyl 2-S-hexanoyl amino-3-[4-5-N-t-butyloxycarbonylpiperidin-4-yl)pentylphenyl propionate.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (3H, t), 1.00-1.35 (12H, m), 1.45 (9H, s), 1.50-1.65 (6H, m), 2.15 (2H, t), 2.50-2.65 (4H, m), 3.05 (2H, m), 3.71 (3H, s), 4.04 (2H, m), 4.83 (1H, m), 5.96 (1H, m), 6.98 (2H, d), 7.04 (2H, d).

This ester (0.17 g, 0.32 mmoles) was suspended in 10 ml of 1:1 THF/H_2O and CH_3OH (2 ml), lithium hydroxide hydrate (0.067 g, 1.6 mmoles) was added and the reaction was stirred for 2.0 hours at room temperature. The solvent was then removed and the residue was taken up in H_2O. This was acidified to pH 2-3 with 10% KSO_4, and extracted with EtOAc. The organic extract was washed with brine, dried (Na_2SO_4) and stripped to give 0.050g of the desired acid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (3H, m), 0.95-1.42 (15 H, m), 1.47 (9H, s), 1.50-1.70 (7H, m), 2.18 (2H, m), 2.48-2.72 (5H, m), 5.02-5.30 (2H, m), 4.03 (2H, m), 4.84 (1H, m), 6.05 (1H, m), 7.06 (4H, s).

This acid (0.15 g, 0.29 mmoles) was dissolved in EtOAc (25 ml), cooled to -70° and treated with HC1 gas for 10 minutes. The temperature was allowed to rise to -20° over 0.5 hr. The reaction mixture was purged with N_2 and the solvent was removed. The residue purified by flash chromatography on silica gel eluting with 9:1:1 EtOH/H_2O/NH_4OH to give pure 8-7, 0.040 g as a white solid.

^{1}H NMR (300 MHz, CD_3OD) δ 0.78 (3H, t), 1.05-1.30 (9H, m), 1.32-1.56 (4H, m), 1.74 (2H, d), 2.03 (2H, m), 2.42 (2H, m), 2.70-2.85 (3H, m), 3.04 (1H, dd), 3.21 (2H, m), 4.38 (1H, m), 6.92 (2H, d), 7.00 (2H, d).

In the above Schemes and Examples, various reagent symbols have the following meanings:

BOC: t-butoxycarbonyl.

Pd-C: Palladium on activated carbon catalyst:

DMF: Dimethylformamide.
CBZ: Benzyloxycarbonyl.
BOP: Benzotriazol-l-yloxytris(dimethylamino)-phosphonium hexafluorophosphate.
EtOAc: ethyl acetate
DMF: dimethylformamide
CH_2Cl_2: methylene chloride
$CHCl_3$: chloroform
MeOH: methanol
HOAc: acetic acid

Suitable alternative protecting groups that can be used in the preparation of the present invention include benzyl ester, cyclohexyl ester, 4-nitrobenzyl ester, t-butyl ester, 4-pyridylmethyl ester, benzyloxycarbonyl, isonicotinyloxycarbonyl, O-chlorobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, t-amyloxycarbonyl, isobornyloxycarbonyl, adamantyloxycarbonyl, 2-(4-biphenyl)-2-propyloxycarbonyl and 9-fluorenylmethoxycarbonyl.

EXAMPLE 58

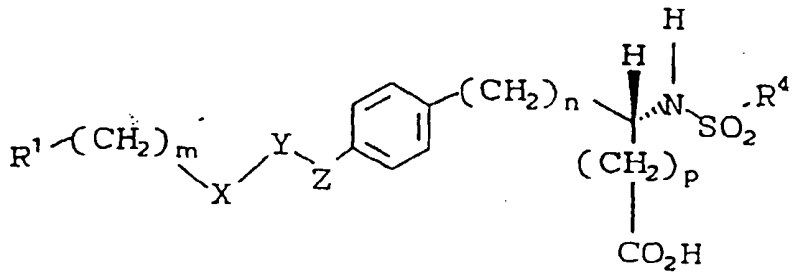
Blood was drawn into 0.1 volumes of acid-citrate-dextrose (85 mM sodium citrate, 64 mM citric acid, 110 mM dextrose) by venipuncture from normal human volunteers. Platelet-rich plasma was prepared by centrifugation at 400 x g for 12 minutes. PGE1 (5 mg/ml) was added and platelets were collected by centrifugation at 800 x g for 12 minutes. The platelet pellet was resuspended into human platelet buffer (140 mM NaCl, 7.9 mM KCl, 3.3 mM Na_2HPO4, 6 mM HEPES, 2% bovine serum albumin, 0.1 % dextrose, pH 7.2) and filtered over Sepharose 2B that was previously equilibrated in human platelet buffer. Platelets were counted and adjusted to 2 x 108/ml with human platelet buffer. Human fibrinogen (10-100 mg/ml and $CaCl_2$ (1 mM) were added and aggregation was initiated by the addition of 10 mM ADP. Aggregation was monitored by the initial rate of increase of light transmittance.

While the invention has been described and illustrated in reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the preferred doses as set forth hereinabove may be applicable as a consequence of variations in the responsiveness of the mammal being treated for severity of clotting disorders or emboli, or for other indications for the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary acording to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention.

Claims

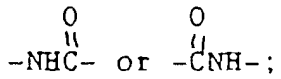
Claims for the following Contracting States : DE, GB, FR, IT, NL, SE, CH, LI, BE, AT, LU, DK

1. A compound of the structural formula



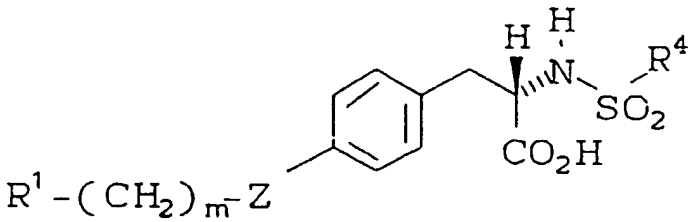
or a pharmaceutically acceptable salt thereof,
wherein

R^1 is		a six member saturated heterocyclic ring containing one or two heteroatoms wherein said heteroatoms are N or 0 and wherein said heterocyclic ring is optionally substituted by C_{1-3} alkyl; or
NR^6R^7		wherin R^6 and R^7 are independently
		hydrogen or
		C_{1-10} alkyl;
R^4 is		aryl,
		C_{1-10} alkyl or
		C_{4-10} aralkyl;
X and Y are		independently
		C_{1-10} alkyl or cycloalkyl,



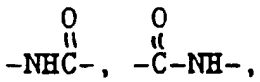
Z is	an optional substituent that, when present, is O, -NHC(O)-, -C(O)NH- or C_{1-5} straight or branched alkyl;
m is	an integer of from zero to six;
n is	one or two; and
p is	zero or one.

2. A compound of the structural formula



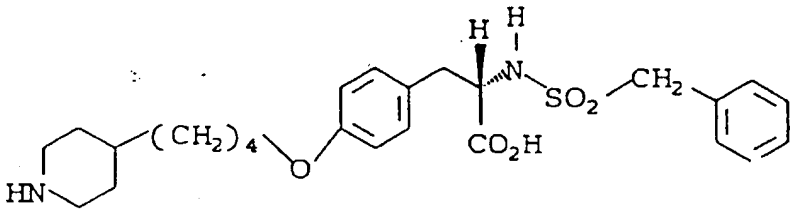
or a pharmaceutically acceptable salt thereof,
wherein

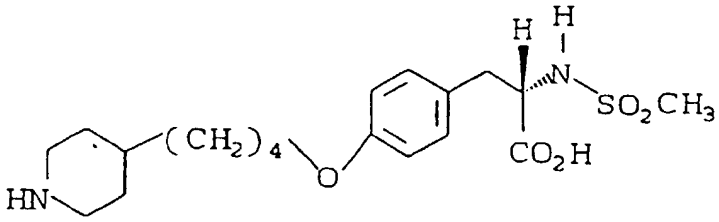
R^1 is	a six member saturated heterocyclic ring containing one or two heteroatoms wherein said heteroatoms are N;
NR^6R^7	wherein R^6 and R^7 are independently
	H or
	C_{1-10} alkyl;
R^4 is	aryl
	C_{1-10} alkyl
	C_{4-10} aralkyl;
Z is	O,

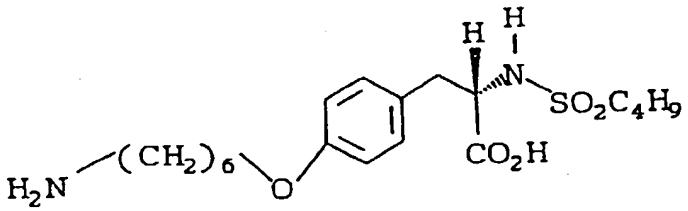


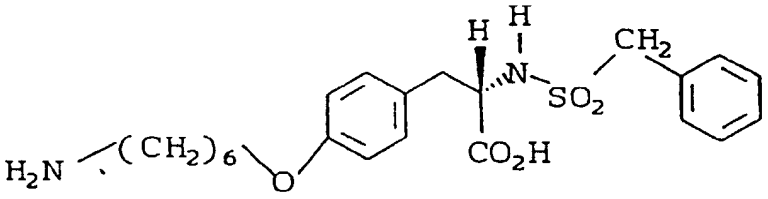
where m is an integer from two to six.

3. A compound as claimed in Claim 2, of the structural formula









or a pharmaceutically acceptable salt thereof.

4. 2-S-(n-Butylsulfonylamino)-3-[4-(piperidin-4-yl)butyloxyphenyl]propionic acid or a pharmaceutically acceptable salt thereof.

5. 2-S-(n-Butylsulfonylamino)-3-[4-(piperidin-4-yl)butyloxyphenyl]propionic acid hydrochloride.

6. A pharmaceutical composition which comprises a compound as claimed in any of claims 1 to 3 and a pharmaceutically acceptable carrier.

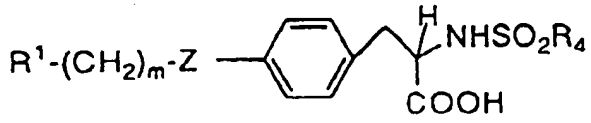
7. A pharmaceutical composition which comprises a compound as claimed in claim 4 and a pharmaceutically acceptable carrier.

8. A pharmaceutical composition which comprises a compound as claimed in claim 5 and a pharmaceutically acceptable carrier.

9. A pharmaceutical composition as claimed in any of claims 6, 7 or 8 adapted for intraveneous, intraperitoneal, subcutaneous or intramuscular administration.

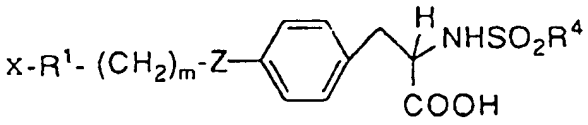
10. The use of a compound as claimed in any of claims 1 to 5 in the manufacture of a medicament for the prevention or treatment of thrombus formation.

11. A process of preparing a compound of formula (I):



(I)

which process comprises deprotecting a compound of formula (II) :



(II)

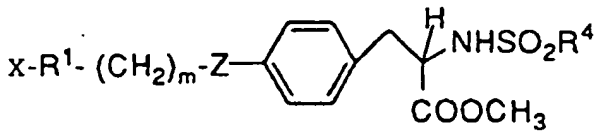
and wherein

R^1 is

a) a six membered saturated heterocyclic ring containing one or two heteroatoms wherein said heteroatoms are N, or
b) NR^6R^7, wherein R^6 and R^7 are independently H or $C_{1\text{-}10}$ alkyl;

R^4 is aryl, $C_{1\text{-}10}$ alkyl or $C_{4\text{-}10}$ aralkyl;
Z is O, -NHC(O)-, or -C(O)NH-;
X is a protecting group; and
m is an integer from 2 to 6.

12. A process according to claim 11, wherein a compound of formula (II) is obtained by hydrolysis of a compound of formula (III):



(III)

13. A process according to claim 11 or 12, wherein protecting group X is selected from the group consisting of benzyl ester, cyclohexyl ester, 4-nitrobenzyl ester, t-butyl ester, 4-pyridylmethyl ester, benzyloxycarbonyl, isonicotinyloxycarbonyl, o-chlorobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, t-amyloxycarbonyl, isobornyloxycarbonyl, adamantyloxycarbonyl, 2-(4-biphenyl)-2-propyloxy-carbonyl and 9-fluorenylmethoxycarbonyl.

14. A process according to any of claims 11 to 13, wherein

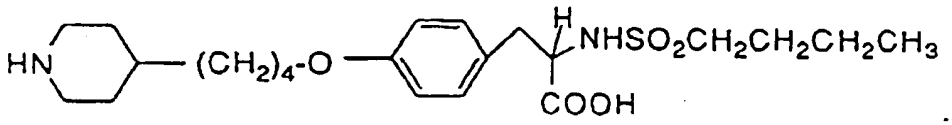
R^1 is a six membered saturated heterocyclic ring containing one heteroatom wherein said heteroatom is N;

R^4 is C_{1-10} alkyl;
Z is O; and
m is an integer from 2 to 6.

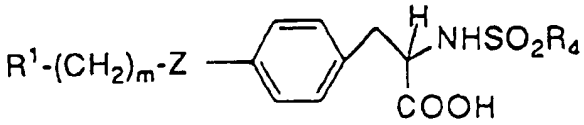
15. A process according to claime 14, wherein

R^1 is a six membered saturated heterocyclic ring containing one heteroatom wherein said heteroatom is N;
R^4 is $-(CH_2)(CH_2)(CH_2)(CH_3)$;
Z is O; and
m is 4.

16. A process of claim 15 wherein the compound of formula I is



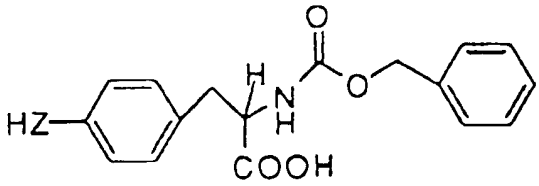
17. A process for making a compound of the following formula:



(I)

which comprises

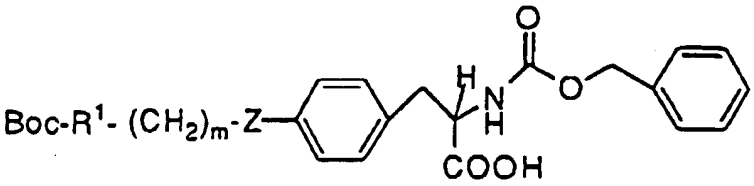
a) reacting N-CBZ-L-tyrosine or derivative thereof having the formula



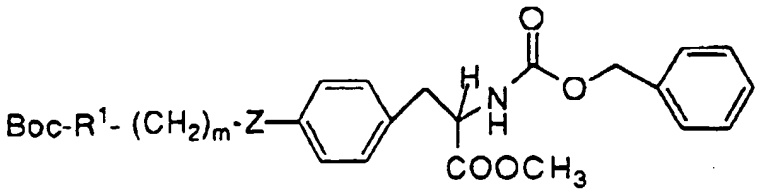
with

$$Boc\text{-}R^1\text{-}(CH_2)_m\text{-}Br$$

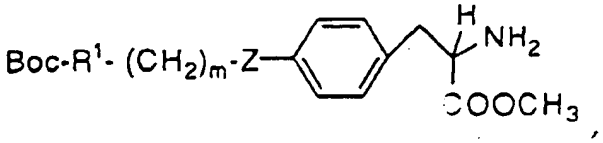
to form



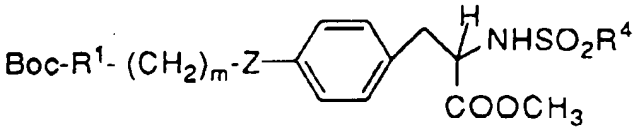
b) reacting the product of a) with methyl iodide to form



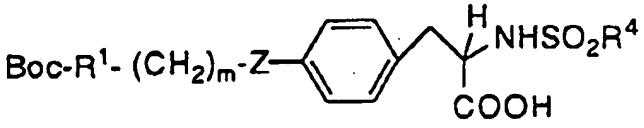
c) reacting the product of b) with ethanol to form



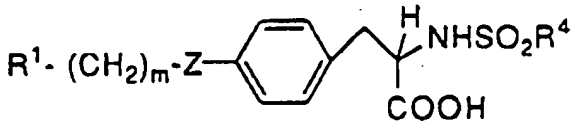
d) reacting the product of c) with $ClSO_2R^4$ to form



e) hydrolyzing the product of d) to form



and
f) deprotecting the product of e) to form



wherein

R^1 is

a) a six membered saturated heterocyclic ring containing one or two heteroatoms wherein said heteroatoms are N, or

b) NR^6R^7, wherein R^6 and R^7 are independently H or $C_{1\text{-}10}$ alkyl;

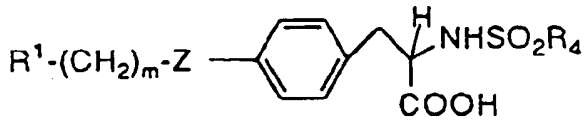
R^4 is aryl, C_{1-10} alkyl, or C_{4-10} aralkyl;

Z is O, -NHC(O)-, or -C(O)NH-; and

m is an integer from 2 to 6.

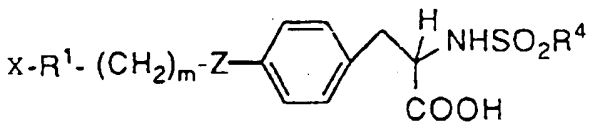
Claims for the following Contracting States : GR, ES

1. A process of preparing a compound of formula (I):



(I)

which process comprises deprotecting a compound of formula (II):



(II)

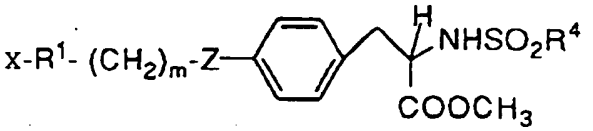
and wherein

R^1 is

a) a six membered saturated heterocyclic ring containing one or two heteroatoms wherein said heteroatoms are N, or
b) NR^6R^7, wherein R^6 and R^7 are independently H or C_{1-10} alkyl;

R^4 is aryl, C_{1-10} alkyl or C_{4-10} aralkyl;
Z is O, -NHC(O)-, or-C(O)NH-;
X is a protecting group; and
m is an integer from 2 to 6.

2. A process according to claim 1, wherein a compound of formula (II) is obtained by hydrolysis of a compound of formula (III):



(III)

3. A process according to claim 1 or 2, wherein protecting group X is selected from the group consisting of benzyl ester, cyclohexyl ester, 4-nitrobenzyl ester, t-butyl ester, 4-pyridylmethyl ester, benzyloxycarbonyl, isonicotinyloxycarbonyl, O-chlorobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, t-amyloxycarbo-

nyl, isobornyloxycarbonyl, adamantyloxycarbonyl, 2-(4-biphenyl)-2-propyloxy-carbonyl and 9-fluorenylmethoxy-carbonyl.

4. A process according to any of claims 1 to 3, wherein

R^1 is a six membered saturated heterocyclic ring containing one heteroatom wherein said heteroatom is N;

R^4 is C_{1-10} alkyl;

Z is O; and

m is an integer from 2 to 6.

5. A process according to claim 4, wherein

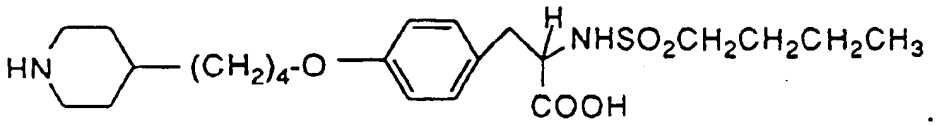
R^1 is a six membered saturated heterocyclic ring containing one heteroatom wherein said heteroatom is N;

R^4 is $-(CH_2)(CH_2)(CH_2)(CH_3)$;

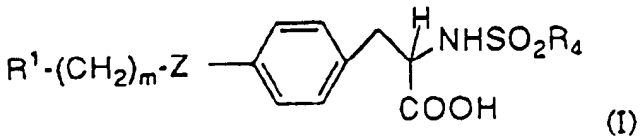
Z is O; and

m is 4.

6. A process of claim 5 wherein the compound of formula I is



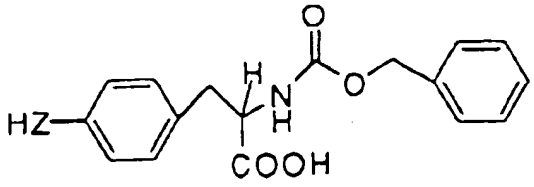
7. A process for making a compound of the following formula:



(I)

which comprises

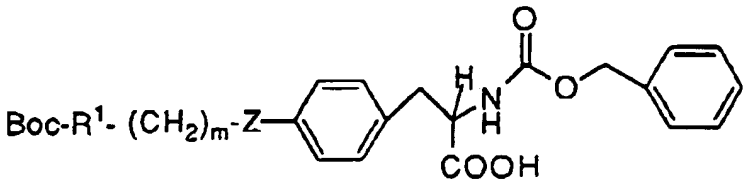
a) reacting N-CBZ-L-tyrosine or derivative thereof having the formula



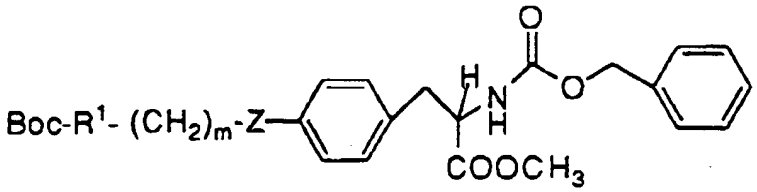
with

$Boc\text{-}R^1\text{-}(CH_2)_m\text{-}Br$

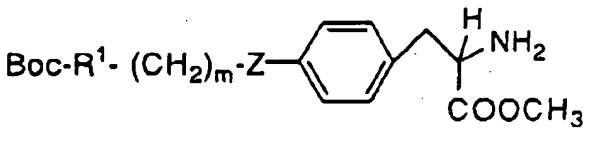
to form



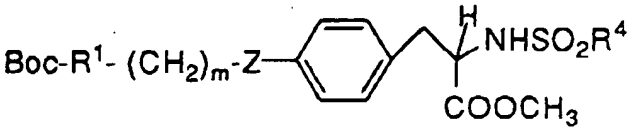
b) reacting the product of a) with methyl iodide to form



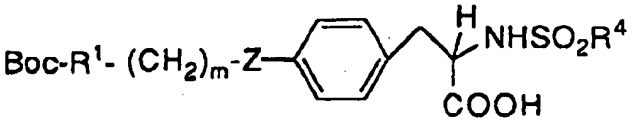
c) reacting the product of b) with ethanol to form



d) reacting the product of c) with $ClSO_2R^4$ to form

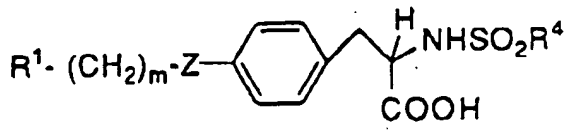


e) hydrolyzing the product of d) to form



and

f) deprotecting the product of e) to form



wherein

R^1 is

a) a six membered saturated heterocyclic ring containing one or two heteroatoms wherein said heteroatoms are N, or
b) NR^6R^7, wherein R^6 and R^7 are independently H or C_{1-10} alkyl;

R^4 is aryl, C_{1-10} alkyl, or C_{4-10} aralkyl;

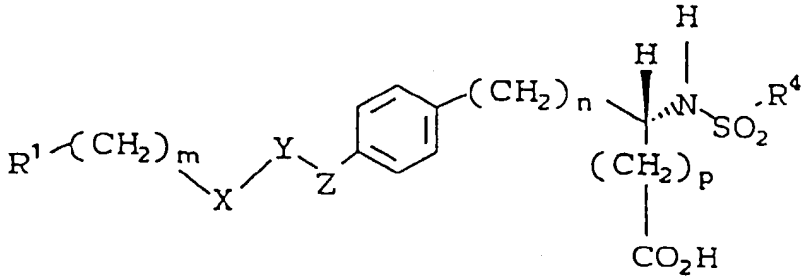
Z is O, -NHC(O)-, or -C(O)NH-; and

m is an integer from 2 to 6.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : DE, GB, FR, IT, NL, SE, CH, LI, BE, AT, LU, DK

1. Eine Verbindung der Strukturformel



oder ein pharmazeutisch annehmbares Salz davon,
worin

R^1 ein sechsgliedriger gesättigter heterocyclischer Ring mit ein oder zwei Heteroatomen, wobei die Heteroatome N oder O sind und der heterocyclische Ring gegebenenfalls durch C_{1-3}-Alkyl substituiert ist, oder NR^6R^7, worin R^6 und R^7 unabhängig voneinander Wasserstoff oder C_{1-10}-Alkyl sind, ist,

R^4 Aryl, C_{1-10}-Alkyl oder C_{4-10}-Aralkyl ist,

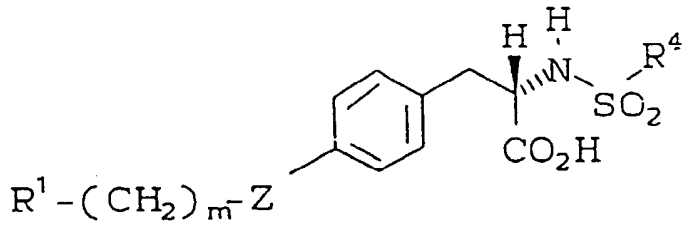
X und Y unabhängig voneinander C_{1-10}-Alkyl oder Cycloalkyl,

sind,

Z ein fakultativer Substituent ist, der, wenn vorhanden, O, -NHC(O)-, -C(O)NH- oder geradkettiges oder

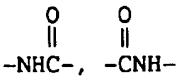
verzweigtes C_{1-5}-Alkyl ist,
m ein ganze Zahl von null bis sechs ist,
n eins oder zwei ist, und
p null oder eins ist.

2. Eine Verbindung der Strukturformel



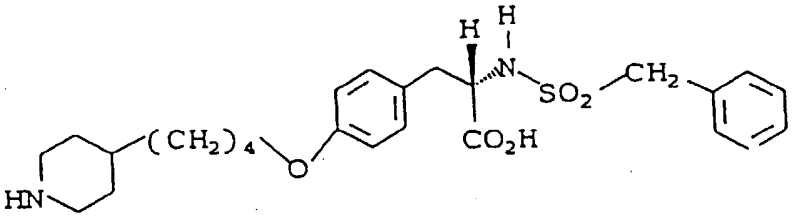
oder ein pharmazeutisch annehmbares Salz davon, worin

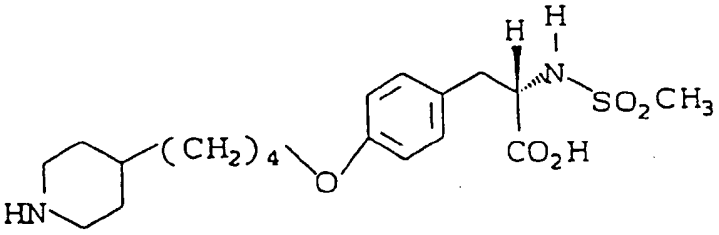
R^1 ein sechsgliedriger gesättigter heterocyclischer Ring mit ein oder zwei Heteroatomen, wobei die Heteroatome N sind, NR^6R^7, worin R^6 und R^7 unabhängig voneinander H oder C_{1-10}-Alkyl sind, ist,
R^4 Aryl, C_{1-10}-Alkyl, C_{4-10}-Aralkyl ist,
Z O,

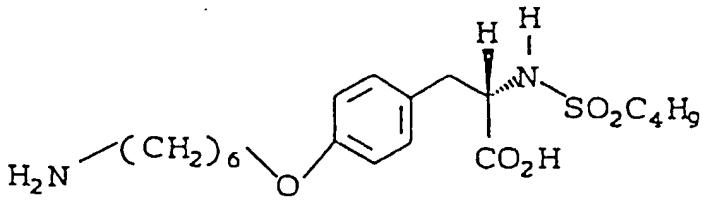


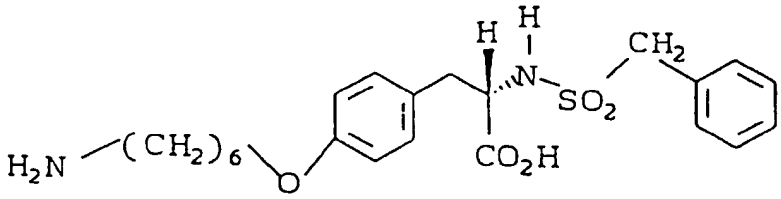
ist, wobei m ein ganze Zahl von zwei bis sechs ist.

3. Eine Verbindung wie in Anspruch 2 beansprucht der Strukturformel









oder ein pharmazeutisch annehmbares Salz davon.

4. 2-S-(n-Butylsulfonylamino)-3-[4-(piperidin-4-yl)butyloxyphenyl]propionsäure oder ein pharmazeutisch annehmbares Salz davon.

5. 2-S-(n-Butylsulfonylamino)-3-[4-(piperidin-4-yl)butyloxyphenyl]propionsäure-Hydrochlorid.

6. Eine pharmazeutische Zusammensetzung, die eine wie in irgendeinem der Ansprüche 1 bis 3 beanspruchte Verbindung und einen pharmazeutisch annehmbaren Träger enthält.

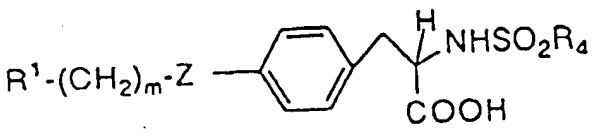
7. Eine pharmazeutische Zusammensetzung, die eine wie in Anspruch 4 beanspruchte Verbindung und einen pharmazeutisch annehmbaren Träger enthält.

8. Eine pharmazeutische Zusammensetzung, die eine wie in Anspruch 5 beanspruchte Verbindung und einen pharmazeutisch annehmbaren Träger enthält.

9. Eine pharmazeutische Zusammensetzung wie in irgendeinem der Ansprüche 6, 7 oder 8 beansprucht, hergerichtet zur intravenösen, intraperitonealen, subkutanen oder intramuskulären Verabreichung.

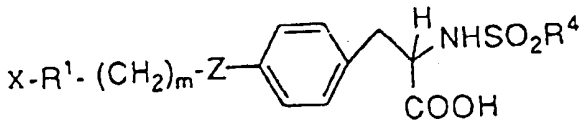
10. Die Verwendung einer wie in irgendeinem der Ansprüche 1 bis 5 beanspruchten Verbindung bei der Herstellung eines Medikaments zur Verhinderung oder Behandlung von Thrombusbildung.

11. Ein Verfahren zur Herstellung einer Verbindung der Formel (I):



(I)

wobei das Verfahren das Entfernen einer Schutzgruppe von einer Verbindung der Formel (II) umfaßt:



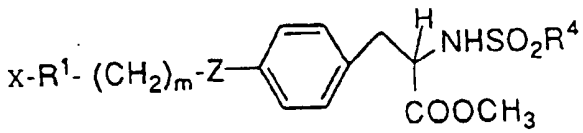
(II)

und worin

R^1 a) ein sechsgliedriger gesättigter heterocyclischer Ring mit ein oder zwei Heteroatomen, wobei die Heteroatome N sind, oder
b) NR^6R^7, worin R^6 und R^7 unabhängig voneinander H oder C_{1-10}-Alkyl sind, ist,

R^4 Aryl, C_{1-10}-Alkyl oder C_{4-10}-Aralkyl ist,
Z O, -NHC(O)- oder -C(O)NH- ist,
X eine Schutzgruppe ist, und
m eine ganze Zahl von 2 bis 6 ist.

12. Ein Verfahren gemäß Anspruch 11, worin eine Verbindung der Formel (II) durch Hydrolyse einer Verbindung der Formel (III) erhalten wird:



(III)

13. Ein Verfahren gemäß Anspruch 11 oder 12, worin die Schutzgruppe X ausgewählt ist aus der Gruppe, bestehend aus Benzylester, Cyclohexylester, 4-Nitrobenzylester, t-Butylester, 4-Pyridylmethylester, Benzyloxycarbonyl, Isonicotinyloxycarbonyl,o-chlorbenzyloxycarbonyl,p-Nitrobenzyloxycarbonyl, p-Methoxybenzyloxycarbonyl, t-Amyloxycarbonyl, Isobornyloxycarbonyl, Adamantyloxycarbonyl, 2-(4-Biphenyl)-2-propyloxycarbonyl und 9-Fluorenylmethoxycarbonyl.

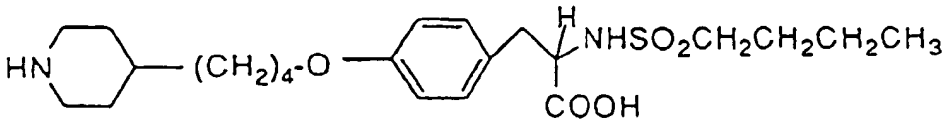
14. Ein Verfahren gemäß irgendeinem der Ansprüche 11 bis 13, worin

R^1 ein sechsgliedriger gesättigter heterocyclischer Ring mit einem Heteroatom ist, wobei das Heteroatom N ist,
R^4 C_{1-10}-Alkyl ist,
Z O ist, und
m eine ganze Zahl von 2 bis 6 ist.

15. Ein Verfahren gemäß Anspruch 14, worin

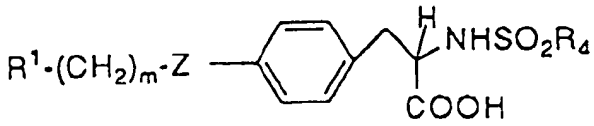
R^1 ein sechsgliedriger gesättigter heterocyclischer Ring mit einem Heteroatom ist, wobei das Heteroatom N ist,
R^4 $-(CH_2)(CH_2)(CH_2)(CH_3)$ ist,
Z O ist, und
m 4 ist.

16. Ein Verfahren nach Anspruch 15, worin die Verbindung der Formel (I)



ist.

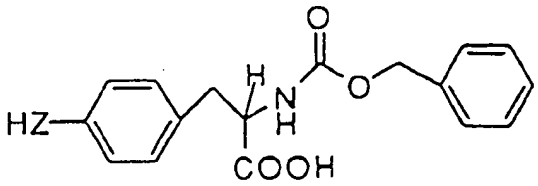
17. Ein Verfahren zur Herstellung einer Verbindung der folgenden Formel:



(I),

welches umfaßt:

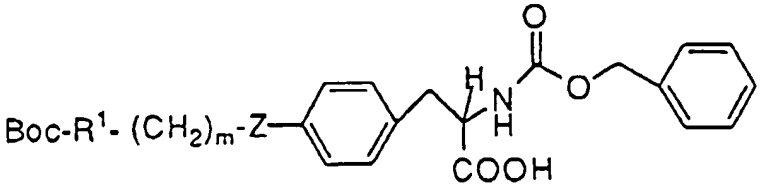
a) Umsetzen von N-CBZ-L-Tyrosin oder einem Derivat davon mit der Formel



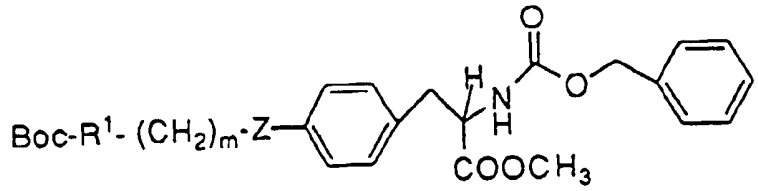
mit

$$Boc\text{-}R^1\text{-}(CH_2)_m\text{-}Br,$$

um

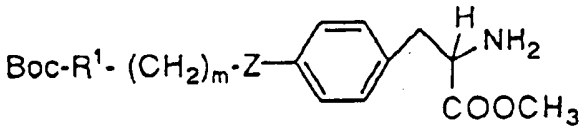


zu bilden,
b) Umsetzen des Produkts aus a) mit Methyliodid, um



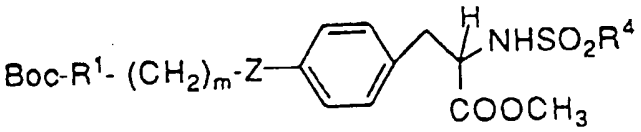
zu bilden,

c) Umsetzen des Produkts aus b) mit Ethanol, um



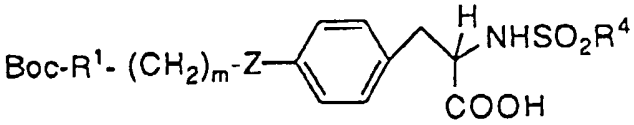
zu bilden,

d) Umsetzen des Produkts aus c) mit $ClSO_2R^4$, um



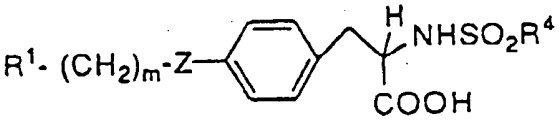
zu bilden,

e) Hydrolysieren des Produkts aus d), um



zu bilden, und

f) Entfernen der Schutzgruppe von dem Produkt aus e), um



zu bilden, worin

R^1 a) ein sechsgliedriger gesättigter heterocyclischer Ring mit ein oder zwei Heteroatomen, wobei die Heteroatome N sind, oder
b) NR^6R^7, worin R^6 und R^7 unabhängig voneinander H oder C_{1-10}-Alkyl sind, ist,

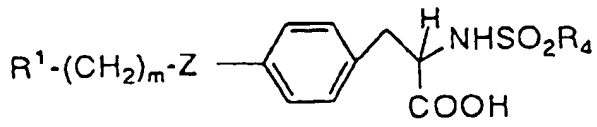
R^4 Aryl, C_{1-10}-Alkyl oder C_{4-10}-Aralkyl ist,

Z O, -NHC(O)- oder -C(O)NH- ist, und

m eine ganze Zahl von 2 bis 6 ist.

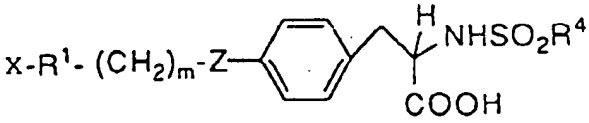
Patentansprüche für folgende Vertragsstaaten : GR, ES

1. Ein Verfahren zur Herstellung einer Verbindung der Formel (I):



(I)

wobei das Verfahren das Entfernen einer Schutzgruppe von einer Verbindung der Formel (II) umfaßt:



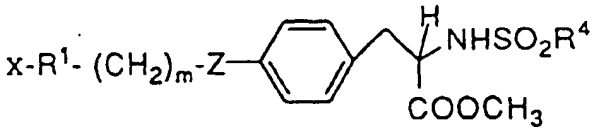
(II)

und worin

R^1 a) ein sechsgliedriger gesättigter heterocyclischer Ring mit ein oder zwei Heteroatomen, wobei die Heteroatome N sind, oder
b) NR^6R^7, worin R^6 und R^7 unabhängig voneinander H oder C_{1-10}-Alkyl sind, ist,

R^4 Aryl, C_{1-10}-Alkyl oder C_{4-10}-Aralkyl ist,
Z O, -NHC(O)- oder -C(O)NH- ist,
X eine Schutzgruppe ist, und
m eine ganze Zahl von 2 bis 6 ist.

2. Ein Verfahren gemäß Anspruch 1, worin eine Verbindung der Formel (II) durch Hydrolyse einer Verbindung der Formel (III) erhalten wird:



(III)

3. Ein Verfahren gemäß Anspruch 1 oder 2, worin die Schutzgruppe X ausgewählt ist aus der Gruppe, bestehend aus Benzylester, Cyclohexylester, 4-Nitrobenzylester, t-Butylester, 4-Pyridylmethylester, Benzyloxycarbonyl, Isonicotinyloxycarbonyl, o-Chlorbenzyloxycarbonyl, p-Nitrobenzyloxycarbonyl, p-Methoxybenzyloxycarbonyl, t-Amyloxycarbonyl, Isobornyloxycarbonyl, Adamantyloxycarbonyl, 2-(4-Biphenyl)-2-propyloxycarbonyl und 9-Fluorenylmethoxycarbonyl.

4. Ein Verfahren gemäß irgendeinem der Ansprüche 1 bis 3, worin

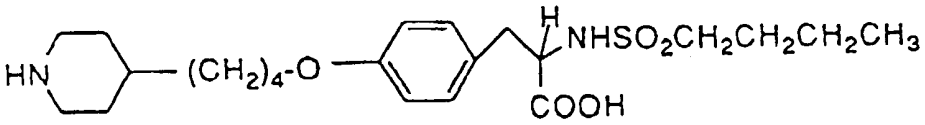
R^1 ein sechsgliedriger gesättigter heterocyclischer Ring mit einem Heteroatom ist, wobei das Heteroatom N ist,
R^4 C_{1-10}-Alkyl ist,
Z O ist, und

m eine ganze Zahl von 2 bis 6 ist.

5. Ein Verfahren gemäß Anspruch 4, worin

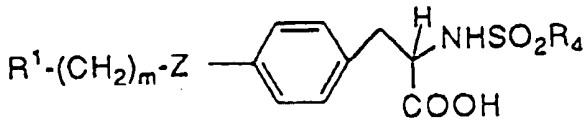
R^1 ein sechsgliedriger gesättigter heterocyclischer Ring mit einem Heteroatom ist, wobei das Heteroatom N ist,
R^4 $-(CH_2)(CH_2)(CH_2)(CH_3)$ ist,
Z O ist, und
m 4 ist.

6. Ein Verfahren nach Anspruch 5, worin die Verbindung der Formel (I)



ist.

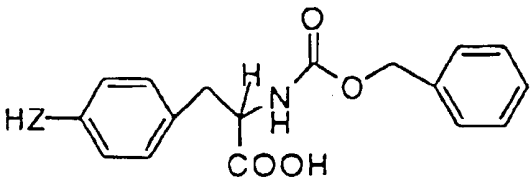
7. Ein Verfahren zur Herstellung einer Verbindung der folgenden Formel:



(I),

welches umfaßt:

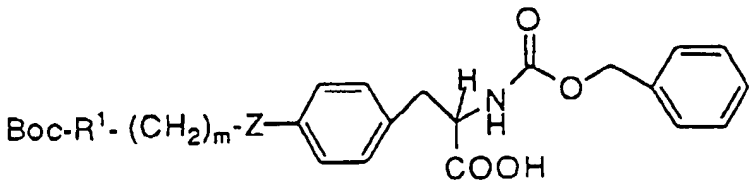
a) Umsetzen von N-CBZ-L-Tyrosin oder einem Derivat davon mit der Formel



mit

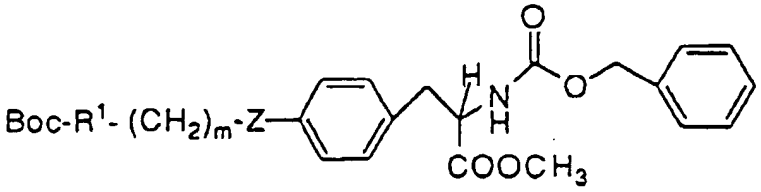
$Boc\text{-}R^1\text{-}(CH_2)_m\text{-}Br$,

um



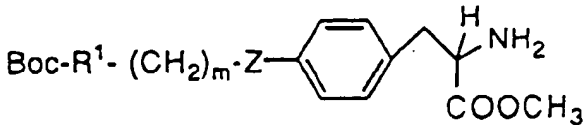
zu bilden,

b) Umsetzen des Produkts aus a) mit Methyliodid, um



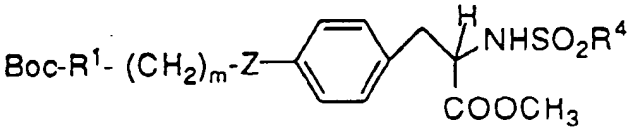
zu bilden,

c) Umsetzen des Produkts aus b) mit Ethanol, um



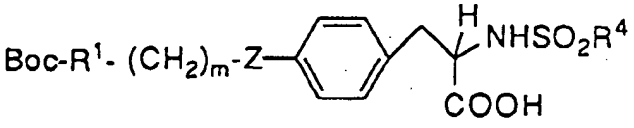
zu bilden,

d) Umsetzen des Produkts aus c) mit $ClSO_2R^4$, um



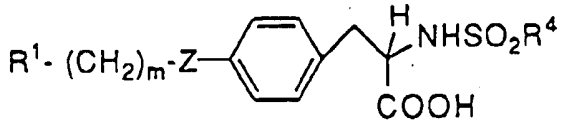
zu bilden,

e) Hydrolysieren des Produkts aus d), um



zu bilden, und

f) Entfernen der Schutzgruppe von dem Produkt aus e), um



zu bilden, worin

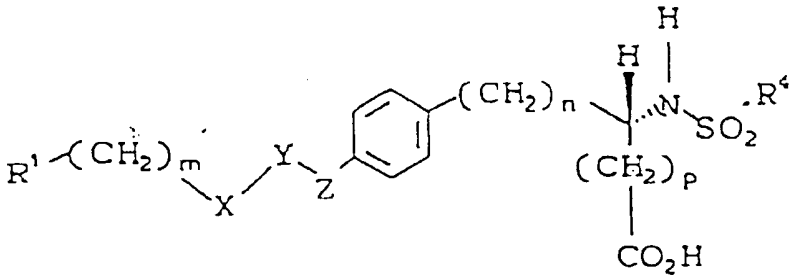
R^1 a) ein sechsgliedriger gesättigter heterocyclischer Ring mit ein oder zwei Heteroatomen, wobei die Heteroatome N sind, oder
b) NR^6R^7, worin R^6 und R^7 unabhängig voneinander H oder C_{1-10}-Alkyl sind, ist,

R^4 Aryl, C_{1-10}-Alkyl oder C_{4-10}-Aralkyl ist,
Z O, -NHC(O)- oder -C(O)NH- ist, und
m eine ganze Zahl von 2 bis 6 ist.

Revendications

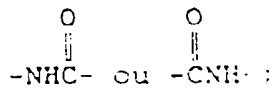
Revendications pour les Etats contractants suivants : DE, GB, FR, IT, NL, SE, CH, LI, BE, AT, LU, DK

1. Composé de formule développée



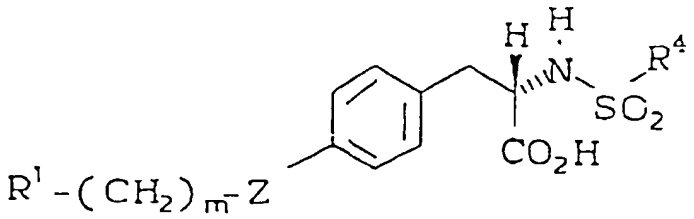
ou un de ses sels acceptables d'un point de vue pharmaceutique, où :

R^1 est un noyau hétérocyclique saturé à 6 chaînons contenant un ou deux hétéroatomes, où lesdits hétéroatomes sont N ou O, et où ledit noyau hétérocyclique est éventuellement substitué par des groupes alkyles en C_{1-3} ; ou encore NR^6R^7, où R^6 et R^7 sont chacun indépendamment l'un de l'autre un hydrogène ou un groupe alkyle en C_{1-10} ;
R^4 est un groupe aryle, alkyle en C_{1-10} ou aralkyle en C_{4-10} ;
X et Y sont chacun indépendamment l'un de l'autre un groupe alkyle ou cycloalkyle en C_{1-10},



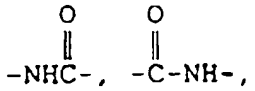
Z est un substituant facultatif qui, quand il est présent, est O, NHC(O), -C(O)NH- ou un groupe alkyle à chaîne droite ou ramifiée en C_{1-5} ;
m est entier valant de 0 à 6 ;
n vaut 1 ou 2 ; et
p vaut 0 ou 1.

2. Composé de formule développée



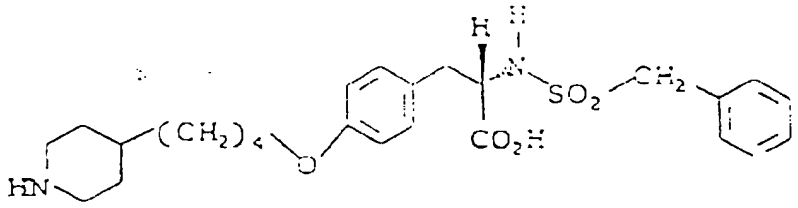
ou un de ses sels acceptables d'un point de vue pharmaceutique, où

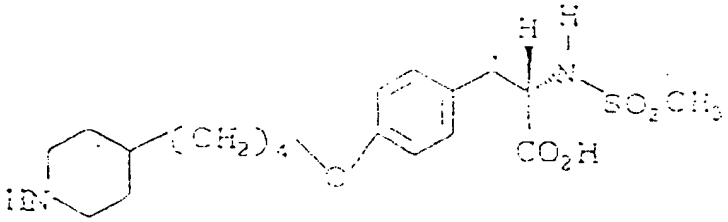
R^1 est un noyau hétérocyclique saturé à six chaînons contenant un ou deux hétéroatomes, où lesdits hétéroatomes sont N ; NR^6R^7, où R^6 et R^7 sont chacun indépendamment l'un de l'autres H ou un groupe alkyle en C_{1-10} ;
R^4 est un groupe aryle, alkyle en C_{1-10} ou aralkyle en C_{4-10} ;
Z est O,

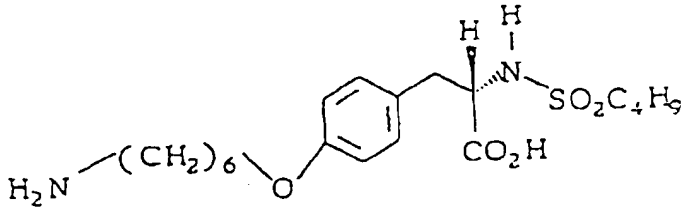


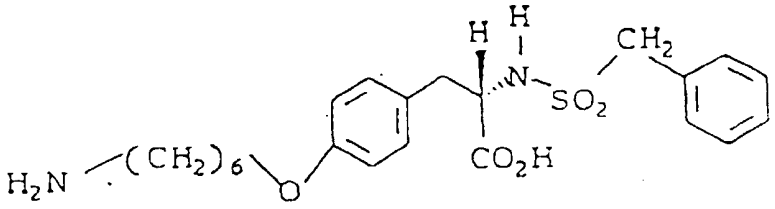
où m est un entier de 2 à 6.

3. Composé selon la revendication 2, ayant la formule développée suivante :









ou l'un de ses sels acceptables d'un point vue pharmaceutique.

4. Acide 2-S-(n-butylsulfonylamino)-3-[4-(pipéridine-4-yl)butyloxyphényl]propionique ou l'un de ses sels acceptables d'un point vue pharmaceutique.

5. Chlorhydrate de l'acide 2-S-(n-butylsulfonylamino)-3-[4-(pipéridine-4-yl)butyloxyphényl]propionique.

6. Composition pharmaceutique qui comprend un composé selon l'une quelconque des revendications 1 à 3 et un support acceptable d'un point vue pharmaceutique.

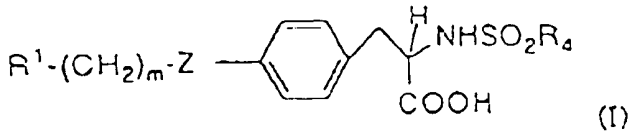
7. Composition pharmaceutique, qui comprend un composé selon la revendication 4 et un support acceptable d'un point vue pharmaceutique.

8. Composition pharmaceutique qui comprend un composé selon la revendication 5 et un support acceptable d'un point vue pharmaceutique.

9. Composition pharmaceutique selon l'une quelconque des revendications 6, 7 ou 8, adapté à une administration intraveineuse, intrapéritonéale, sous-cutanée ou intramusculaire.

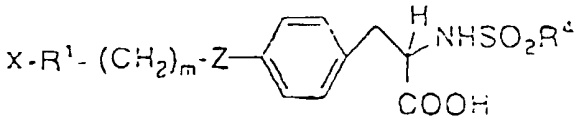
10. Utilisation d'un composé selon l'une quelconque des revendications 1 à 5 pour fabriquer un médicament destiné à la prévention ou au traitement de la formation de thrombus.

11. Procédé pour préparer un composé de formule (I)



(I)

lequel procédé consiste à déprotéger un composé de formule (II)



(II)

et où

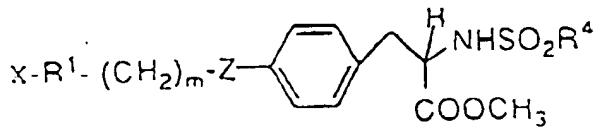
R^1 est

a) un noyau hétérocyclique saturé à six chaînons contenant un ou deux hétéroatomes, où lesdits hétéroatomes sont N , ou

b) NR^6R^7, où R^6 et R^7 sont chacun, indépendamment l'un de l'autres H ou un groupe alkyle en C_{1-10} ;

R^4 est un groupe alkyle, alkyle en C_{1-10} ou aralkyle en C_{4-10} ;
Z est O, -NHC(O)-, -C(O)-NH- ;
X est un groupe protecteur ; et
où m est un entier de 2 à 6.

12. Procédé selon la revendication 11, dans lequel on obtient un composé de formule (II) par hydrolyse d'un composé de formule (III)



(III)

13. Procédé selon la revendication 11 ou 12, dans lequel le groupe protecteur X est choisi parmi l'ensemble comprenant l'ester benzylique, l'ester cyclohexylique, l'ester 4-nitrobenzylique, l'ester tert-butylique, l'ester 4-pyridylbutylique, les groupes benzyloxycarbonyle, isonicotinyloxycarbonyle, O-chlorobenzyloxycarbonyle, p-nitrobenzyloxycarbonyle, p-méthoxybenzyloxycarbonyle, tert-amyloxycarbonyle, isobornyloxycarbonyle, adamantyloxycarbonyle, 2-(4-biphényl)-2-propyloxycarbonyle et 9-fluorénylméthoxycarbonyle.

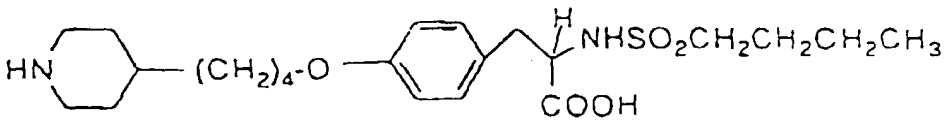
14. Procédé selon l'une quelconque des revendications 11 à 13, dans lequel :

R^1 est un noyau hétérocyclique saturé à 6 chaînons contenant un hétéroatome, où ledit hétéroatome est N ;
R^4 est groupe alkyle en C_{1-10} ;
Z est O ; et
m est un entier de 2 à 6.

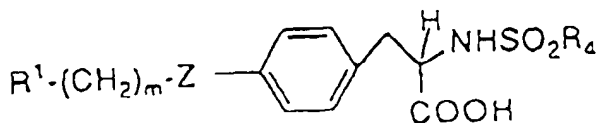
15. Procédé selon la revendication 14 dans lequel

R^1 est un noyau hétérocyclique saturé à 6 chaînons, contenant un hétéroatome, où ledit hétéroatome est N ;
R^4 est $-(CH_2)(CH_2)(CH_2)(CH_3)$;
Z est O ; et
m vaut 4.

16. Procédé selon la revendication 15, dans lequel le composé de formule (I) est le composé suivant :



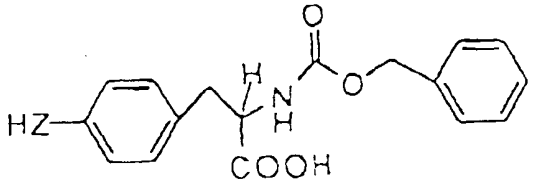
17. Procédé pour préparer un composé ayant la formule suivante :



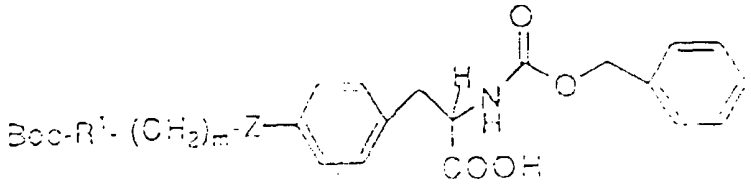
(I)

qui consiste

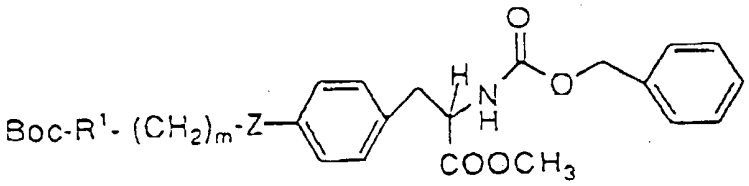
a) à faire réagir de la N-CBZ-L-tyrosine, ou l'un de ses dérivés, ayant la formule suivante :



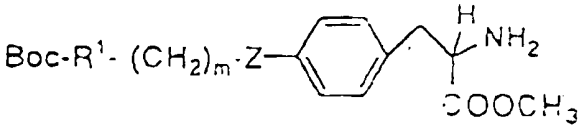
avec
$Boc\text{-}R^1\text{-}(CH_2)_m\text{-}Br$
pour former



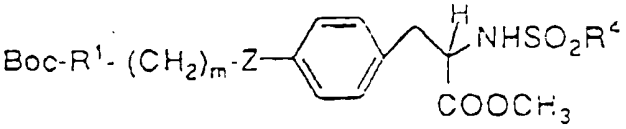
b) à faire réagir le produit de a) avec de l'iodure de méthyle, pour former



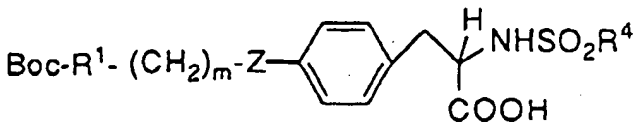
c) à faire réagir le produit de b) avec de l'éthanol pour former



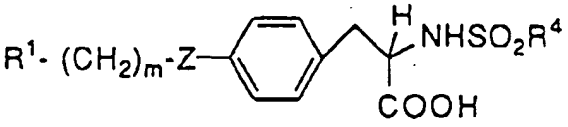
d) à faire réagir le produit de c) avec du $ClSO_2R^4$ pour former



e) à hydrolyser le produit de d) pour former



f) et à déprotéger le produit de e) pour former



où

R^1 est

a) un noyau hétérocyclique saturé à six chaînons contenant un ou deux hétéroatomes, où lesdits hétéroatomes sont N , ou
b) NR^6R^7, où R6 et R7 sont chacun indépendamment l'un de l'autres H ou un groupe alkyle en C_{1-10} ;

R^4 est un groupe aryle, alkyle en C_{1-10} ou aralkyle en C_{4-10} ;

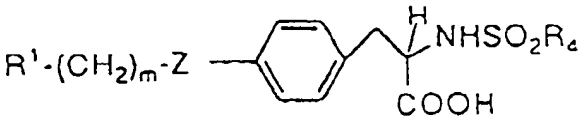
Z est O, -NHC(O)-, -C(O)-NH- ;

X est un groupe protecteur ; et

où m est un entier de 2 à 6.

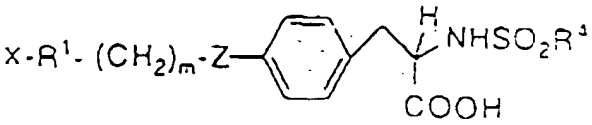
Revendications pour les Etats contractants suivants : GR, ES

1. Procédé pour préparer un composé de formule (I)



(I)

lequel procédé consiste à déprotéger un composé de formule (II)



(II)

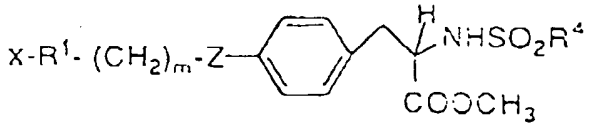
et où

R^1 est

a) un noyau hétérocyclique saturé à six chaînons contenant un ou deux hétéroatomes, où lesdits hétéroatomes sont N, ou
b) NR^6R^7, où R^6 et R^7 sont chacun indépendamment l'un de l'autres H ou un groupe alkyle en C_{1-10} ;

R^4 est un groupe aryle, alkyle en C_{1-10} ou aralkyle en C_{4-10} ;
Z est O, -NHC(O)-, -C(O)-NH- ;
X est un groupe protecteur ; et
où m est un entier de 2 à 6.

2. Procédé selon la revendication 11, dans lequel on obtient un composé de formule (II) par hydrolyse d'un composé de formule (III)



(III)

3. Procédé selon la revendication 11 ou 12, dans lequel le groupe protecteur X est choisi parmi l'ensemble comprenant l'ester benzylique, l'ester cyclohexylique, l'ester 4-nitrobenzylique, l'ester tert-butylique, l'ester 4-pyridylbutylique, les groupes benzyloxycarbonyle, isonicotinyloxycarbonyle, O-chlorobenzyloxycarbonyle, p-nitrobenzyloxycarbonyle, p-méthoxybenzyloxycarbonyle, tert-amyloxycarbonyle, isobornyloxycarbonyle, adamantyloxycarbonyle, 2-[4-biphényl)-2-propyloxycarbonyle et 9-fluorénylméthoxycarbonyle.

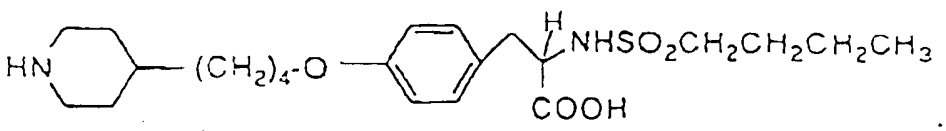
4. Procédé selon l'une quelconque des revendications 11 à 13, dans lequel :

R^1 est un noyau hétérocyclique saturé à 6 chaînons contenant un hétéroatome, où ledit hétéroatome est N ;
R^4 est un groupe alkyle en C_{1-10} ;
Z est O ; et
m est un entier de 2 à 6.

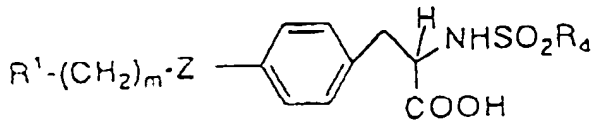
5. Procédé selon la revendication 14 dans lequel

R^1 est un noyau hétérocyclique saturé à 6 chaînons, contenant un hétéroatome, où ledit hétéroatome est N;
R^4 est $-(CH_2)(CH_2)(CH_2)(CH_3)$;
Z est O ; et
m vaut 4.

6. Procédé selon la revendication 15, dans lequel le composé de formule (I) est le composé suivant :



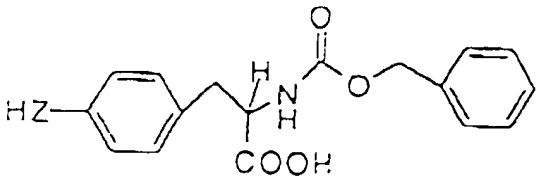
7. Procédé pour préparer un composé ayant la formule suivante :



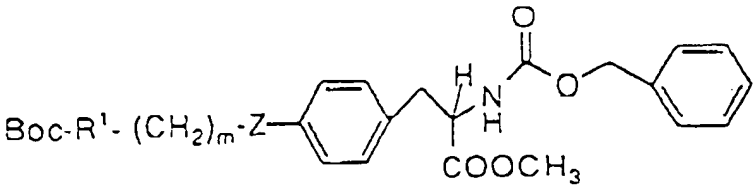
(I)

qui consiste

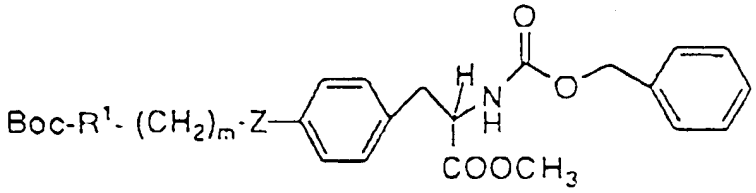
a) à faire réagir de la N-CBZ-L-tyrosine, ou l'un de ses dérivés, ayant la formule suivante :



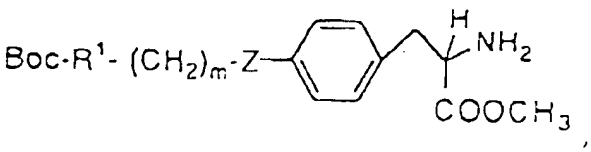
avec
Boc-R^1-$(CH_2)_m$-Br
pour former



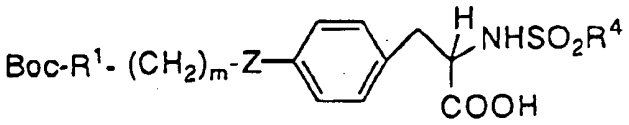
b) à faire réagir le produit de a) avec de l'iodure de méthyle, pour former



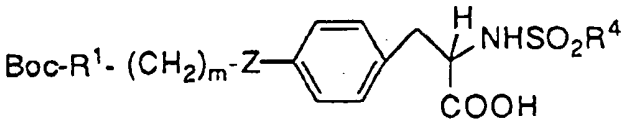
c) à faire réagir le produit de b) avec de l'éthanol pour former



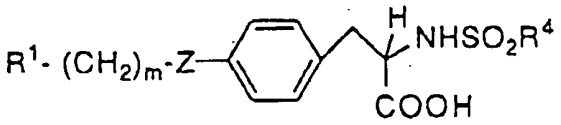
d) à faire réagir le produit de c) avec du $ClSO_2R^4$ pour former



e) à hydrolyser le produit de d) pour former



f) et à déprotéger le produit de e) pour former



où

R^1 est

a) un noyau hétérocyclique saturé à six chaînons contenant un ou deux hétéroatomes, où lesdits hétéroatomes sont N , ou
b) NR^6R^7, où R6 et R7 sont chacun indépendamment l'un de l'autres H ou un groupe alkyle en C_{1-10} ;

R^4 est un groupe aryle, alkyle en C_{1-10} ou aralkyle en C_{4-10} ;
Z est O, -NHC(O)-, -C(O)-NH- ;
X est un groupe protecteur ; et
où m est un entier de 2 à 6.